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Proposed Re-evaluation Decision

Dithiopyr

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Overview

Proposed Re-evaluation Decision for Dithiopyr

After a re-evaluation of the herbicide dithiopyr, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing dithiopyr for sale and use in Canada.

An evaluation of available scientific information found that under the proposed conditions of use, products containing dithiopyr have value and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of dithiopyr, new risk-reduction measures are proposed for the labels of all products. No additional data are being requested at this time.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing dithiopyr registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for dithiopyr and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of dithiopyr.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (see contact information on the cover page of this document).

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of Dithiopyr Affect Human Health?

Dithiopyr is unlikely to affect your health when used according to the revised label directions.

Potential exposure to dithiopyr may occur through the drinking water, when handling and applying the product or when entering treated areas such as residential turf and golf courses. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when dithiopyr products are used according to label directions.

Dithiopyr induced mild but transient eye and dermal irritation in rabbits and was not a sensitizer in guinea pigs. Consequently, no statements are required on the label of the technical product.

Dithiopyr did not cause cancer in animals, was not genotoxic or teratogenic and showed no signs of neurotoxicity. The liver and kidneys were the main targets of toxicity by the oral route in mice, rats and dogs. Effects on liver weights were also seen following exposure via the dermal route in rats. There is a low level of concern for potential prenatal and postnatal toxicity associated with dithiopyr.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water

Dietary risks from water are not of concern.

As dithiopyr is not registered for use on food, exposure and risk from food consumption is considered negligible. Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to dithiopyr was estimated from residues in drinking water and ranged from 6.5% of the acceptable daily intake for the general population to 21.2% of the acceptable daily intake for infants. An acute drinking water assessment was not performed as no acute endpoints were identified, due to the low acute toxicity of dithiopyr.

Risks in Residential and Other Non-occupational Environments

Non-occupational risks are not of concern.

Risks to homeowners applying the domestic product are not of concern. Postapplication risks to adults, youths and children entering treated lawns and turf following commercial and homeowner application are not of concern.

Aggregate risks are not of concern.

Aggregate risks to homeowners and children from drinking water and residential exposures are not of concern

Occupational Risks From Handling Dithiopyr

Occupational risks are not of concern.

Risk estimates associated with applying, mixing and loading activities are not of concern and additional personal protective equipment are not required beyond what is currently specified on the label.

Postapplication risks are not of concern.

Risks to workers re-entering turf treated with dithiopyr are not of concern. The minimum 12 hour restricted-entry interval (REI) is proposed for all uses, with the exception of golf courses where entry is restricted until after the spray has dried.

Environmental Considerations

What Happens When Dithiopyr Is Introduced Into the Environment?

Dithiopyr poses a potential risk to terrestrial and aquatic plants; therefore, additional risk-reduction measures need to be observed.

When dithiopyr is released into the environment, some of it can be found in soil and surface water. However, dithiopyr readily volatilizes from turf grass, is broken down by soil microbes and undergoes phototransformation in water. Thus, dithiopyr is not expected to persist in the environment. Laboratory and field studies indicate that dithiopyr is not mobile in soil. There is limited potential for leaching and groundwater contamination and runoff can occur, although the concentrations are low.

When dithiopyr is used for weed control in turf grass, there is a potential that non-target plant species on land and in water may be exposed to the chemical as a result of spray drift or runoff. Some of plant species are sensitive to the chemical and would be adversely affected. To minimize the potential exposure, strips of land between the agricultural field and the nontarget terrestrial or aquatic areas must be left unsprayed. The width of these buffer zones will be specified on the product label. Dithiopyr presents negligible risk to wild birds and mammals, bees and other arthropods. Dithiopyr poses risk to terrestrial plants and aquatic organisms like fish, amphibians and algae. The concentrations are very low in runoff and do not pose a concern for aquatic environments.

Value Considerations

What Is the Value of Dithiopyr?

Dithiopyr controls crabgrass in turf.

Crabgrass is a troublesome weed in turf. Dithiopyr provides both pre-emergence and early postemergence control of crabgrass in established turf. It provides a wider application window than alternative crabgrass control products used on turf. In addition, the application rate of dithiopyr is usually lower than that of alternative crabgrass control products.

Measures to Minimize Risk

Additional Key Risk-Reduction Measures

Human Health

- Additional label statements to clarify the maximum number of applications per year
- A restricted-entry interval to protect workers entering treated sites

Environment

- Precautionary statements and buffer zones to protect non-target terrestrial and aquatic habitats and terrestrial and aquatic habitats that may contain sensitive species

Next Steps

Before making a re-evaluation decision on dithiopyr, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

At the time that the re-evaluation decision is made, the PMRA will publish an Evaluation Report on dithiopyr in the context of this re-evaluation decision (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

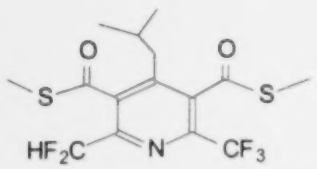
1.0 Introduction

Dithiopyr is a selective turf herbicide. It belongs to the pyridine chemical family and is classified as a Group 3 herbicide. Dithiopyr is an inhibitor of microtubule assembly, inhibiting plant cell divisions.

Following the re-evaluation announcement for dithiopyr, Dow AgroSciences Canada Inc., the registrant of the technical grade active ingredient and primary data provider in Canada, indicated support for all uses included on the label of the Commercial Class end-use product. There are no Domestic Class end-use products containing dithiopyr.

2.0 The Active Substance, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Dithiopyr
Function	Herbicide
Chemical family	Pyridine
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	S,S'-dimethyl 2-difluoromethyl-4-isobutyl-6-trifluoromethylpyridine-3,5-dicarbothioate
2 **Chemical Abstracts Service (CAS)**	
CAS Registry Number	97886-45-8
Molecular formula	$C_{15}H_{16}F_5NO_2S_2$
Structural formula	
Molecular weight	401.4 amu

Identity of relevant impurities of human health or environmental concern	Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 139, No. 24, SI/2005-114 (30 November 2005), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	0.53 mPa
Ultraviolet (UV)/visible spectrum	Not provided
Solubility in water at 20°C	1.4 mg/L
n-octanol–water partition coefficient	4.75
Dissociation constant	Not applicable

2.3 Description of Registered Dithiopyr Uses

Appendix I lists all dithiopyr products that are registered under the authority of the *Pest Control Products Act*, including one technical grade active ingredient, one manufacturing concentrate and one commercial class end-use product.

Appendix II lists all uses for which dithiopyr is presently registered. The registrant supported all uses when the re-evaluation was initiated; therefore, all uses were considered in the health and environmental risk assessments.

Uses of dithiopyr belong to a single use-site category, being turf. Dithiopyr is mainly used on golf courses and residential lawns in Ontario and Quebec.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for dithiopyr was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes with the exception of an in vivo chromosomal aberration study. All of the toxicity studies were conducted in accordance with accepted international testing protocols and good laboratory practice in place at that time. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

In acute toxicity studies, dithiopyr is of low toxicity by the oral, dermal and inhalation routes of exposure. Dithiopyr induced mild but transient eye and dermal irritation in rabbits and was not a sensitizer in guinea pigs.

Results from toxicokinetic studies indicated that absorption was dose-dependent in rats; the higher the dose, the lower the fraction absorbed. Dithiopyr was rapidly and extensively metabolized by rats with the major end-products being carboxylic acids and thioacids. Study results indicate that whether administered by oral or intravenous dose, fat retains the greatest fraction of dithiopyr. Delayed clearance of dithiopyr was noted with the majority of radioactivity eliminated between 72 and 96 hours postdosing.

Both the urinary and fecal metabolic profiles differed between sexes following acute exposure. Metabolic profiles also differed in the male animals depending on whether the route of exposure was oral or intravenous; however, diacids IV and V were continuously detected. Despite the route, dosage or dosing regimen, female rats routinely excreted more carbon 14 (^{14}C) through urine than their male counterparts. Conversely, male rats appeared to have more active biliary excretion of dithiopyr. Neither the metabolic pattern nor the distribution of metabolites in rats were changed following repeat dose protocols.

In repeat-dose dietary studies in rats and mice, dose-related alterations were noted in organ weights and histopathology predominantly involving the liver and kidneys. Altered pathology mainly involving the liver and the kidneys was also noted in repeat-dose studies in dogs exposed orally (by capsule) to dithiopyr. Increased liver weights were also seen following exposure via the dermal route in rats. Repeat-dose inhalation studies were not available. Throughout the subchronic oral studies, decreased food efficiency, elevated alkaline phosphatase, reduced hemoglobin and reduced hematocrit levels were common findings, with both liver and kidney appearing to be the target organs. No gender sensitivities were seen in repeat-dose dietary studies. Comparison of the dietary short and long-term toxicity studies suggested a pronounced increase in toxicity with increased duration of dosing.

In the multigeneration rat reproduction study, no effects were noted in either the parents or offspring at the lowest dose examined. However, at the next dosage level, alterations in liver pathology were noted in pups from both generations that were not seen in the parental animals at the same dose level. A high incidence of white spots on the surface of liver lobes was noted in mid-dose (males only) and high-dose pups from both generations. Among mid-dose and high-dose second filial generation (F_2) pups dying during lactation days 0 to 4 or culled on lactation day 4, an increased incidence of focal hepatocellular necrosis and fibrosis was noted. F_2 pups that died during lactation days 5 to 21 or were killed after weaning experienced a high incidence of fibrosis and mineralization with no signs of necrosis. First filial generation (F_1) pups at weaning showed a treatment-related increase in fibrosis, but not necrosis, as adults these animals showed neither fibrosis nor necrosis.

The white spots on the liver surface were identified as focal hepatocellular necrosis and fibrosis/mineralization. While the pups were growing, the incidence of necrosis appeared to be tapering off with no signs of necrosis identified in the weanlings. In contrast, the incidence of fibrosis/mineralization in the weanlings was increased. Based on these findings, the theory was put forward by the study author that necrotic lesions were followed by fibrosis and mineralization during the growth of pups, with the lesions becoming small and obscure by the time of weaning. Given these pathological alterations occurring in the F_2 pups were more severe than the hepatic lesions noted in the parental animals and occurred at doses eliciting minimal parental systemic toxicity, there is evidence of sensitivity of the young to dithiopyr. No information is available to indicate whether this sensitivity would be present with other routes of dosing.

Dithiopyr's effects on reproductive parameters in the multigeneration rat reproduction study were limited to decreased birth weights. Dithiopyr did not induce developmental changes or teratogenic effects in either rats or rabbits following in utero exposure, even at maternally toxic doses. Effects on the endocrine system were noted in the adrenals, thyroid and pituitary but only at high dose levels which elicited significant systemic toxicity.

Dithiopyr was considered non-mutagenic based on the negative results obtained in Ames tests (*Salmonella* strains TA98, 100, 1535, 1537 and 1538) with and without metabolic activation, a Chinese Hamster Ovary/Hypoxanthine-Guanine Phosphoribosyl Transferase gene mutation assay, an in vitro cytogenetic assay and an in vitro hepatocyte DNA repair (unscheduled DNA synthesis) assay. Dithiopyr did not show evidence of carcinogenicity in the mouse or rat.

A single oral dose of dithiopyr given to rabbits in a pharmacology study did not affect respiration rate, blood pressure, heart rate or electrocardiogram results.

Results of the acute and chronic tests conducted on laboratory animals with Dithiopyr Technical, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix III, Table 1 and 2.

***Pest Control Products Act* Hazard Characterization**

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, extensive data were available for dithiopyr. Data of high quality were available for dithiopyr and included a developmental toxicity study in rats, a developmental toxicity study in rabbits and a multigeneration reproduction study in rats.

With respect to potential prenatal and postnatal toxicity, developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of fetuses to in utero exposure. In the two-generation rat reproduction study, sensitivity of the young was noted based on the presence of hepatic alterations (white spots, focal hepatocellular necrosis) in pups that were more severe than the lesions noted in the parental animals. However, as the pups aged, the presence of these hepatic lesions improved to the point that they were undetectable in adult animals. Given the hepatic lesions appeared to have no long-term implications, there is a low level of concern for potential prenatal and postnatal toxicity associated with dithiopyr.

3.2 Occupational and Non-occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

Risks from different routes of exposure were aggregated using an aggregate risk index (ARI). Risks greater than one do not require risk mitigation. If the calculated ARI is less than one, it does not necessarily mean that exposure will result in adverse effects. However, ARIs less than one require measures to mitigate (reduce) risk.

3.2.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk-Assessment

Acute Endpoints
Due to the low acute toxicity of dithiopyr, toxicological endpoints for an acute dermal and inhalation risk assessment are not required.

Short-Term and Intermediate-Term Dermal Risk Assessments
For residential and occupational short-term dermal assessment relative to the use pattern (1–30 days), the NOAEL of 1000 mg/kg bw/day (the highest dose tested) from the 21-day dermal toxicity study in rabbits was selected. Given the dermal toxicity study was conducted solely on adult animals, there is uncertainty whether or not the sensitivity observed with oral exposures to the young would also be manifested via the dermal route. The multigeneration reproduction study in rats revealed that sensitivity may occur in the fetus or nursing infant as a result of an indirect exposure via the mother.

This is a concern because the population (including workers) could include pregnant or lactating women, who could potentially pass an indirect dose of dithiopyr to their offspring. Given the lack of appropriate dermal data (to confirm or refute the sensitivity), a threefold uncertainty factor in the form of a database deficiency is considered appropriate to protect the young. The target MOE selected for all populations when using this study is 300, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and an additional 3-fold uncertainty factor for database deficiency. For residential exposure, the

Pest Control Products Act factor was reduced to onefold as database uncertainties were subsumed under the applied uncertainty factors.

For occupational intermediate-term dermal assessment relative to the use pattern (1 month to several months), the NOAEL of 1000 mg/kg bw/day (the highest dose tested) from the 21-day dermal toxicity study in rabbits was selected. The target MOE selected when using this study is 1000, thus accounting for standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and an additional 10-fold uncertainty factor. The latter factor was employed for the lack of information on sensitivity of the young by the dermal route and extrapolation of the results from a short-term study to a longer-term exposure scenario.

Short-Term and Intermediate-Term Inhalation Risk Assessments

As there are no repeat-dose inhalation studies available for inhalation risk exposure, it is appropriate to assume that absorption via inhalation exposure is equivalent to oral absorption.

For residential and occupational short-term and intermediate-term exposure (up to 3 months), the 13-week dietary toxicity study in the rat was chosen with a NOAEL of 0.7 mg/kg bw/day. As this study NOAEL was lower than that of the multigeneration reproduction study (NOAEL of 1.9 mg/kg bw/day) in which sensitivity of the young was observed, the NOAEL was considered protective of the effects noted in the young animals. The target MOE selected for all populations when using this study is 100, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential exposure, the *Pest Control Products Act* factor was reduced to onefold as the toxicity database was considered complete and there was a low level of concern for potential prenatal and postnatal toxicity with dithiopyr.

Non-Dietary Short-term Oral Ingestion

For assessing non-dietary short-term oral ingestion in children entering treated lawns and turf (1–7 days), the offspring NOAEL of 1.9 mg/kg bw/day in a two-generation rat reproduction study (liver pathology at 16.4 mg/kg bw/day) was chosen with a target MOE of 100 (10-fold uncertainty factor for interspecies extrapolation and 10-fold uncertainty factor for intraspecies variability). The *Pest Control Products Act* factor was reduced to onefold as the toxicity database was considered complete and there was a low level of concern for potential prenatal and postnatal toxicity with dithiopyr.

Endpoint for Biomonitoring Risk Assessment

Where exposure (short-term to intermediate-term) has been assessed via biomonitoring, the selected toxicological endpoint is the NOAEL of 0.7 mg/kg bw/day from the 13-week dietary toxicity study in the rat, with a target MOE of 100. Biomonitoring studies take into account contributions from dermal, inhalation and oral (including non-dietary incidental oral) routes of exposure. Thus, exposure and risk assessments using this endpoint are considered more protective than the route-specific endpoints and accompanying MOEs.

Dermal Absorption

A dermal absorption value was not required for this assessment as dermal toxicity studies were selected for the dermal risk assessment.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to dithiopyr through mixing, loading or applying the pesticide and/or when entering a treated site to conduct activities such as scouting and/or handling of treated turf.

Mixer, Loader and Applicator Exposure and Risk Assessment
There are potential exposures to mixers, loaders, and applicators. The following supported uses were assessed:

- Mixing/loading emulsifiable concentrates
- Groundboom application to golf courses and sod farms
- Mixing/loading/applying by backpack to residential turf, golf courses and sod farms
- Mixing/loading/applying by turf gun to residential turf, golf courses and sod farms

Based on the number of applications, workers applying dithiopyr would generally have a short-term to intermediate-term (one to several months) duration of exposure. The PMRA estimated handler exposure based on the following level of personal protection:

- Baseline personal protective equipment (PPE) – long pants, a long-sleeved shirt, shoes plus socks and chemical-resistant gloves (unless specified otherwise). For groundboom application, this scenario does not include gloves as the data quality were better for non-gloved scenarios than gloved scenarios.

Mixer/loader/applicator exposure estimates are based on the best available data at this time.

A chemical-specific handler biomonitoring study was submitted for dithiopyr. This study was conducted with commercial applicators applying dithiopyr to residential turf. Eighteen lawn care specialists applied dithiopyr at a rate of 1.12 kg a.i./ha to approximately 0.8 ha of residential turf during the course of a normal working day. A spray gun attached to large tank on a truck was used for application. All workers wore long pants and short-sleeved shirts and some also wore a variety of other protective equipment such as face shields, safety glasses and hats. Only two of the applicators reported wearing gloves during application, although all wore gloves during mixing and loading (open-pour). Complete 24-hour urine samples were collected from each worker for three days following application. A monkey pharmacokinetic study conducted using dithiopyr was submitted to the PMRA. The study was considered acceptable and was used to interpret the biomonitoring study results. Worker exposure ranged from 0.0260 to 0.216 µg/kg bw/day. The maximum exposure value was used in the risk assessment for workers using turf guns on residential lawns; this is considered to be a high-end estimate of exposure. As the application rate used in the biomonitoring study is twice that registered in Canada, the exposure from this study is considered to be conservative relative to the potential exposure to Canadian applicators.

For those scenarios where no acceptable chemical-specific handler exposure data were submitted, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. The PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the

generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE.

Occupational risk estimates associated with applying, mixing and loading dithiopyr for application to residential and commercial turf meet the target MOE, and ARIs are greater than one at baseline PPE. Therefore, risk to workers handling dithiopyr was not of concern. See Appendix IV for risk estimate calculations.

Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated turf. Based on the dithiopyr use pattern, there is potential for short-term (< 30 days) postapplication exposure to dithiopyr residues for workers.

Chemical-specific turf transferrable residue (TTR) data and activity-specific transfer coefficients (TCs) were used to estimate postapplication exposure resulting from contact with treated turf at various times after application. TTR data include the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. A TC is a factor that relates worker exposure to transferrable residues. TCs are specific to a given crop and activity combination (e.g. hand harvesting apples or scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Postapplication exposure activities include harvesting, thinning, pruning, scouting and irrigating.

For workers entering a treated site, REIs are calculated to determine the minimum length of time required before people can safely re-enter. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE (i.e. > 300 for short-term dermal exposure scenarios for dithiopyr). See Appendix IV for risk estimate calculations.

A TTR study performed using both granular and liquid formulations to turf was submitted to the PMRA. Maximum liquid and granular mean TTR values from the day of application were used to estimate occupational and residential postapplication exposure.

All postapplication scenarios had MOEs that were above the target MOE on the day of application and therefore not of concern. Mitigation beyond the minimum 12-hour REI is not required. See Appendix IV for risk estimate calculations.

A turf volatility study was submitted to the PMRA. This study reported that up to 38% of the applied product can volatilize within 30 days of application. Although this study was considered unacceptable for risk-assessment purposes due to major limitations including low recovery and minimal study validation, these data were considered in a screening level assessment, the results of which would determine if further data would be required. The maximum concentration of volatilized dithiopyr measured in the study (7.82 $\mu g/m^3$) was used to conduct an inhalation-specific risk assessment. As the application rate used in this study is twice that which is registered in Canada, the dithiopyr air concentration is considered to be a high-end estimate. Inhalation exposure was then aggregated with the maximum dermal MOE from entry on the day of application. The MOE for the conservative inhalation exposure scenario was above the target

MOE. When combined with the highest dermal MOEs, the resulting ARI was greater than one. Thus, postapplication risk is not of concern. See Appendix IV for risk estimate calculations.

3.2.3 Non-Occupational Exposure and Risk Assessment

Non-occupational risk assessment involves estimating risks to the general population, including children, during or after pesticide application, and assumes that homeowners wear short pants, a short-sleeved shirt and no gloves. Increased clothing will decrease the exposure and risk to homeowners during or after application.

Residential Mixer, Loader and Applicator Exposure and Risk Assessment
Dithiopyr is also included in some pesticide-fertilizer products regulated by the Canadian Food Inspection Agency.

Homeowners can apply granular pesticide-fertilizer products in the spring and early summer to residential turf. Given homeowners can only apply the product once during the spring and early summer, they have potential for short-term exposure to dithiopyr.

There is the potential for homeowners to mix, load and apply domestic class pesticide-fertilizer products. The following supported uses were assessed:

- Loading granular pesticide-fertilizer
- Applying granules by hand to residential turf
- Mixing/loading/applying granules by push-rotary spreader to residential turf
- Mixing/loading/applying granules by belly grinder to residential turf

No acceptable chemical-specific handler exposure data were submitted for homeowners applying dithiopyr on turf; therefore, dermal and inhalation exposures were estimated using data from the PHED, Version 1.1, and Outdoor Residential Exposure Task Force (ORETF) studies. The ORETF studies monitored exposure to workers and homeowners mixing/loading and applying pest control products to turf. Monitoring was conducted using passive dosimetry, including hand washes, face/neck wipes and personal air samplers.

Non-occupational risk estimates associated with mixing, loading and applying dithiopyr to residential turf meets the target MOE and ARIs are greater than one, thus residential use was not of concern. See Appendix IV for risk estimate calculations.

Postapplication Non-Occupational Exposure and Risk Assessment

There is potential for short-term exposure to adults, youth and children entering treated lawns and turf. Adults and youth have the potential for dermal and inhalation exposure, while children also have the potential for incidental oral exposure. It is assumed that people enter the treated area immediately after application.

Dermal Exposure
Dermal postapplication exposure is estimated in the same way as occupational postapplication exposure where a chemical-specific TTR data and activity-specific TCs are used.

A TTR study performed using both granular and liquid formulations to turf was submitted to the PMRA. Maximum liquid and granular mean TTR values from the day of application were used to estimate residential postapplication exposure.

A chemical-specific passive dosimetry study for postapplication activities on turf performed in conjunction with the TTR study was also submitted to the PMRA. Ninety-six participants were monitored for dermal exposure performing various activities (specifically children's activity patterns) on turf treated with liquid or granular formulation. Dermal exposure was monitored using whole body dosimeters. The highest mean exposure values from granular and liquid formulations were used in the postapplication risk assessment for residential turf. As this study was conducted with adults, exposures were normalized for body weight and surface area for youth and children.

Dermal MOEs were above the target MOE for all scenarios and subpopulations and therefore not of concern. See Appendix IV for risk estimate calculations.

Inhalation Exposure
A turf volatility study was submitted to the PMRA. This study reported that up to 38% of the applied product can volatilize within 30 days of application. Although this study was considered unacceptable for risk assessment purposes due to major limitations including low recovery and minimal study validation, these data were considered in a screening level risk assessment to assess potential inhalation exposure for residential post-application activities on treated turf, the results of which would determine if further data would be required. As there is no toxicological endpoint established for an acute inhalation scenario and only one application per year is permitted on residential turf, the average concentration of dithiopyr in air over 30 days was used in the residential postapplication assessment for both liquid and granular formulations. As the application rate used in this study is twice that which is registered in Canada, the dithiopyr air concentration used in this assessment is considered to be a high-end estimate.

The MOE for the inhalation exposure scenario was above the target MOE for all subpopulations and therefore not of concern. See Appendix IV for risk estimate calculations.

Incidental Oral Exposure
Incidental oral exposure through hand-to-mouth, object-to-mouth and ingestion of soil were assessed and aggregated for children; the resulting ARI was greater than one and therefore not of concern. Ingestion of granules is considered to be an acute episodic event and was not required as no acute endpoints were identified due to the low acute toxicity of dithiopyr.

Postapplication Risk: Total Exposure From All Routes

Exposure from all routes of postapplication exposure (dermal, inhalation and incidental oral) were aggregated for all subpopulations, where applicable. The resulting ARIs were greater than one for all scenarios and subpopulations, and therefore not of concern. See Appendix IV for risk estimate calculations.

3.3 Dietary Risk Assessment

As there are no registered food uses of dithiopyr, a dietary risk assessment was not required.

3.4 Exposure from Drinking Water

3.4.1 Determination of Acute Reference Dose

Due to the low acute toxicity of dithiopyr, an acute reference dose is not required.

3.4.2 Determination of Acceptable Daily Intake

To estimate dietary risk from repeat exposure (from drinking water), the most suitable study is a two-year chronic study in the rat. This study resulted in a NOAEL of 0.4 mg/kg bw/day based on the presence of altered liver pathology at the next dosage level of 3.6 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability are used. The *Pest Control Products Act* factor was reduced to 1-fold as the toxicity database was considered complete and there was a low level of concern for potential prenatal and postnatal toxicity with dithiopyr.

$$\text{ADI} = \frac{0.4 \text{ mg/kg bw/day}}{100} = 0.004 \text{ mg/kg bw/day}$$

This acceptable daily intake (ADI) provides a margin of 250 000 to the developmental NOAEL and 475 to the lowest NOAEL for effects in offspring, for parental toxicity and for reproductive toxicity. It is thus considered protective of all populations including pregnant women, infants and children.

3.4.3 Concentrations in Drinking Water

Residues of dithiopyr in drinking water sources in Canada were estimated using the Leaching Estimation and Chemistry Model (LEACHM) and the Pesticide Root Zone Model/Exposure Analysis Modelling System (PRZM/EXAMS). Estimated environmental concentrations (EECs) of dithiopyr in groundwater were calculated using the LEACHM model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using LEACHM are estimates of the flux, or movement, of pesticide into shallow groundwater (2 m or 5 m depth) with time. EECs of dithiopyr in surface water were calculated using the

PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

The EECs predicted by Level 1 modelling were high enough for Level 2 modelling to be conducted. The refinements used for Level 2 modelling were to use a scenario representing Ontario and Quebec only, because the current product registration is limited to those two provinces. For Level 2 surface water modelling, a turf scenario was used together with weather files from Ontario and Quebec instead of the standard Level 1 scenarios. As no dugouts are present in Ontario and Quebec, EECs in surface water were only generated for the reservoir. The Level 2 EECs are thus crop- and region-specific and do not allow for future use expansion into other crops or regions. Table 3.4.3.1 provides the Level 1 and Level 2 modelled EECs for dithiopyr in potential sources of drinking water.

The highest estimated yearly surface water EEC value (12.3 µg a.i./L) was used in the chronic drinking water risk assessment.

Table 3.4.3.1 Level 1 and 2 Estimated Environmental Concentrations of Dithiopyr in Potential Drinking Water Sources

Refinement Level	Groundwater EEC (µg a.i./L)		Surface Water EEC			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Level 1	19	19	28	5.6	63	54.9
Level 2 (Ontario and Quebec only)	12.3	12.3[6]	3.2	2	N/A[5]	N/A[5]

1 90th percentile of daily average concentrations.
2 90th percentile of yearly average concentrations.
3 90th percentile of yearly peak concentrations.
4 90th percentile of yearly average concentrations.
5 Dugout not included as regional scenarios for Ontario and Quebec only were used in Level 2 modelling.
6 Value used in drinking water chronic assessment.

Water Monitoring Data

Limited information on dithiopyr water monitoring data was available for Canada. Two datasets submitted to the PMRA contained data on various pesticide concentrations, including dithiopyr, in 8 Canadian tributaries of Lake Ontario in 2000 and 2001. Of the 195 samples analysed in these two datasets, dithiopyr was not detected.

American databases were searched for detections of dithiopyr. Both databases searched (the United States Geological Survey National Water Quality Assessment [NAWQA] Program and the United States Environmental Protection Agency [USEPA] Storage and Retrieval Database

[STORET]) did not contain information on dithiopyr. The NAWQA Program does not have dithiopyr on the analyte list and no information was submitted to STORET for dithiopyr.

A study was conducted to investigate the impact of lawn-care pesticides on aquatic ecosystems. To determine the impact of lawn-care pesticides on aquatic ecosystems, various pesticides were analysed in the water of six American streams. The limits of quantitation for pesticides in water were set at 0.1 ng/L. Water samples were collected quarterly from the summer 2000 to the spring of 2002 (i.e. 6 samples) from each stream. Dithiopyr was detected in each stream (71–82% detection) with maximum concentrations ranging from 122.7–252.5 ng/L.

3.4.4 Drinking Water Exposure and Risk Assessment

For the chronic drinking water exposure assessment, the estimated dithiopyr concentration in drinking water is multiplied by the water consumption data for all relevant population subgroups to obtain an average daily pesticide exposure value. Dithiopyr concentration estimates in drinking water are based on the highest yearly surface water value modelled (12.3 µg a.i./L). The consumption data are based on the average daily water consumption of the general population and its subgroups. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic drinking water exposure is acceptable.

For all subpopulations, drinking water exposures were below the ADI and, therefore, not of concern. An acute drinking water assessment was not required, as acute endpoints were not identified due to the low acute toxicity of dithiopyr. See Appendix V for risk estimate calculations.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from drinking water, residential and other non-occupational sources from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Aggregate Acute Risk and Exposure Assessment

Due to the low acute toxicity of dithiopyr, aggregate acute risk was not required as no acute endpoints were identified.

3.5.2 Aggregate Short-Term Exposure and Risk Assessment

Short-term aggregate exposure to dithiopyr may be comprised of drinking water and residential (dermal, inhalation and incidental oral) exposures. The relevant duration of exposure for this assessment would likely be for a period less than one month. Liver toxicity was the common toxic effect among all routes of exposure. For the dermal component, the NOAEL of 1000 mg/kg bw/day (highest dose tested) from the 21-day dermal toxicity study in rabbits was selected based on increased liver weights at that dose level. In the absence of repeat-dose inhalation data, it is assumed that liver toxicity would also be a critical endpoint by this route of

exposure and thus deemed appropriate to default to oral studies for the inhalation component. Consequently, the NOAEL of 0.7 mg/kg bw/day from the 13-week oral toxicity study in rats is selected based on increased liver weights and liver pathology at the next higher dose level. This same study and NOAEL was selected to reflect the oral component (incidental oral exposure) of the aggregate assessment. The target MOE of 300 was chosen for the dermal exposure route to account for uncertainties associated with interspecies extrapolation (10-fold), intraspecies variability (10-fold) and the lack of information on sensitivity of the young by the dermal route (3-fold). The target MOE of 100 was considered appropriate for all other exposure routes and populations.

The chronic drinking water exposure is considered representative of a typical dietary exposure because it represents the average daily exposure over an individual's lifetime. This exposure was combined with short-term residential exposure estimated for children, youth and adults. Resulting ARIs were greater than one for all groups and, therefore, not of concern. See Appendix VI for risk estimate calculations.

3.6 Incident Reports

Starting on 26 April 2007, registrants are required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product.

There were no incident reports submitted for dithiopyr as of 27 May 2008.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties (Section 2.2), dithiopyr has low solubility in water, is not likely to volatilize from moist soil or water surfaces under field conditions and has a potential for bioaccumulation in organisms. Environmental fate data for dithiopyr are summarized in Table 1 of Appendix VIII. Dithiopyr is stable to hydrolysis at environmentally relevant pHs. Dithiopyr has high affinity to soil, therefore, is not mobile. Dithiopyr is stable to phototransformation in soil but undergoes phototransformation in the water and air. The major transformation products are the Monoacid, Reverse Monoacid and Diacid (Appendix IX). Dithiopyr is stable to biotransformation in aquatic environments being mostly absorbed into the sediment.

Laboratory studies on adsorption/desorption and soil column leaching indicate that dithiopyr is not mobile in soil. Field studies conducted in Canada detected residues of dithiopyr in only the top 15 cm deep soil layer. Canadian water monitoring data (Appendix VII) have shown no detections of dithiopyr in surface water and in groundwater.

4.2 Effects on Non-Target Species

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models that take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from terrestrial and aquatic habitats, including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible, and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies and probabilistic risk-assessment methods. Refinements to the risk-assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial Organisms

A risk assessment of dithiopyr to terrestrial organisms was based upon an evaluation of toxicity data on dithiopyr to earthworms (acute), bees (acute contact), two species of birds (acute oral, dietary and chronic), two species of mammals (acute oral, dietary and chronic) and ten species of terrestrial plants (seed germination, seedlings emergence and vegetative vigour). A summary of terrestrial toxicity data for dithiopyr is presented in Appendix VIII, Table 2. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with dithiopyr.

Dithiopyr demonstrated no adverse toxicological effects on terrestrial invertebrates and birds on an acute oral, dietary and reproductive basis. Dithiopyr has a potential adverse effect on mammals on chronic basis (dietary and reproductive). As dithiopyr is a herbicide, adverse effects to non-target terrestrial plants are expected. Plant emergence and vegetative vigour studies conducted with ten plant species indicated that, although the seeds of most plant species emerged successfully, plants exposed to dithiopyr did not follow normal growth patterns. No toxicity studies conducted with dithiopyr transformation products were available for review.

The screening level risk assessment in Appendix VIII, Table 3, indicated that exposure to dithiopyr does not pose a risk to terrestrial invertebrates or birds. However, the risk of chronic effects for mammals was identified. As a result, a refinement of the risk assessment was conducted taking into consideration the exposure concentrations of dithiopyr that could be present in terrestrial habitat directly adjacent to the application field through drift of spray. Spray drift data for a medium American Society of Agricultural Engineers (ASAE) droplet size, as is generally used in groundboom applications of herbicides, indicate the maximum amount of spray that will drift one metre down wind from the point of application during spraying is 6%. Using this percent drift, the off-site EECs for dithiopyr were calculated. Based on this refinement, dithiopyr exceedance of the LOC was reduced to 26 times from 427 times. However, taking under consideration that dissipation of dithiopyr from turf grass is relatively quick and that a peak concentration was used in the risk characterization, the expected exposure will be less than the effects endpoints of concern shortly after application. Based on these considerations, the PMRA has concluded that there is minimal risk of chronic effects. Table 4 (Appendix VIII) summarizes the refined risk assessment from dithiopyr to mammals.

As would be expected, the herbicide dithiopyr poses a risk to non-target terrestrial plants. The screening level risk assessment indicated that RQ exceeded the LOC by as much as 192 times. As a result, a refinement of the risk assessment was conducted taking into consideration the concentrations of dithiopyr that could be present in terrestrial habitat directly adjacent to the application field through drift of spray. Based on this method of refinement, dithiopyr poses a reduced risk to non-target terrestrial plants directly adjacent to the application field. Exceedance of the LOC was reduced to 11.5 times from 192 times. Further refinement was conducted using Sensitivity Species Distribution (SSB) analysis which indicated that LOC exceedance was further reduced to 7. Buffer zones will be required to mitigate the risk of dithiopyr to non-target terrestrial plants. Appendix VIII, Table 4 summarizes the refined risk assessment from dithiopyr to non-target terrestrial plants.

4.2.2 Effects on Aquatic Organisms

Risk to aquatic organisms, acute and chronic, is based on an evaluation of toxicity data on dithiopyr for four freshwater species (one invertebrates, two fish and one algae). A summary of aquatic toxicity data for dithiopyr are presented in Appendix VIII, Table 2. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with dithiopyr.

Dithiopyr is toxic to freshwater invertebrates and fish on an acute basis. Dithiopyr shows toxic effects to fish in the early life-cycle study. Acute and early life-cycle toxic effects on amphibians are expected based on surrogate data from fish studies. As dithiopyr is a herbicide, adverse effects to non-target aquatic plants are also expected. Dithiopyr affected biomass and cell density of freshwater algae. Data on aquatic vascular plants were not available.

The risk assessment was conducted using data for the most sensitive freshwater organisms tested *Daphnia magna*, bluegill sunfish (*Lepomis macrochirus*), rainbow trout (*Oncorhynchus mykiss*) and green alga (*Selenastrum capricornutum*).

The screening level risk assessment indicated that dithiopyr does pose a risk to freshwater fish, amphibians (based on surrogate data from fish studies) and algae. The RQs exceeded LOCs by 1.25–8 times at the application rate of 558 g a.i./ha. Thus, a refined risk assessment was triggered. The refined assessment indicated negligible risk as the exceedance of the LOCs are less then 1 from spray drift and from runoff. Table 5 (Appendix VIII) summarizes the risk assessment from dithiopyr to aquatic organisms. In Appendix VIII, Tables 6 and 7 summarize the refined risk to aquatic organisms from dithiopyr spray drift and runoff, respectively.

5.0 Value

5.1 Value of Dithiopyr

Crabgrass is a troublesome weed in turf. Dithiopyr provides both pre-emergence and early postemergence control of crabgrass in established turf. It provides a wider application window than alternative crabgrass control products used in turf. In addition, the application rate of dithiopyr is usually lower than that of alternative crabgrass control products.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's *Toxic Substances Management Policy*, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, dithiopyr was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of dithiopyr were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use products. Dithiopyr and its transformation products were evaluated against the following Track 1 criteria:

- persistence in soil ≥182 days;
- persistence in water ≥182 days;
- persistence in sediment ≥365 days;
- persistence in air ≥2 days;
- bioaccumulation log K_{ow} ≥5; or
- bioconcentration factor (BCF) ≥5000 (or bioaccumulation factor (BAF) ≥5000).

For dithiopyr or its transformation products to meet Track 1 criteria, the criteria for both bioaccumulation and persistence (in one media) must be met. The technical product and end-use product, including formulants, were assessed against the contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern, Part 3 Contaminants of Health or Environmental Concern.

The PMRA has reached the following conclusions.

- Dithiopyr does not meet all Track 1 criteria. Dithiopyr does meet the Track 1 criteria for persistence because the half-life values in air (41 days), water/sediment (390–490 days) and soil (523–2300 days) exceed the TSMP Track 1 criteria for water, sediment and soil. Dithiopyr does not meet the Track 1 criterion for bioaccumulation as its *n*-octanol–water partition coefficient (log K_{ow} 4.75) and BCF (81–930) are below the Track 1 criterion. Although the Track 1 criterion is met for persistence, the Track 1 criterion for bioaccumulation is not met; therefore, dithiopyr does not meet all Track 1 criteria, and is not considered a Track 1 substance.

- Dithiopyr does not form any transformation products that meet the Track 1 criteria.

- There are no Track 1 formulants in the technical product or end-use product.

- There are no Track 1 contaminants in the technical product or end-use product.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, formulants and contaminants in the technical and end-use products are assessed against the formulants and contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern. The following assessment refers to the formulants and contaminants in Part 1 and Part 2 of the list.

Technical grade dithiopyr and the end-use product Dimension Turf Herbicide do not contain any formulants or contaminants of health or environmental concern.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for dithiopyr is adequate to define the majority of toxic effects that may result from exposure to dithiopyr. In rats and rabbits, dithiopyr was not carcinogenic, genotoxic, neurotoxic or teratogenic. There is low level of concern for potential prenatal and postnatal toxicity associated with dithiopyr. The liver and kidneys were the main targets of toxicity by the oral route in mice, rats and dogs. Effects on liver weights were also seen following exposure via the dermal route in rats. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

7.1.1 Occupational Risk

Risk estimates associated with mixing and lo ding and applying dithiopyr are not of concern. Postapplication risks to workers are not of concern; the minimum 12-hour restricted-entry interval (REI) is proposed for all uses, with the exception of golf courses where entry is restricted until the spray has dried.

7.1.2 Dietary Risk from Food

Dithiopyr is not registered for use on food crops, so a dietary risk assessment was not conducted.

7.1.3 Dietary Risk from Drinking Water

Risk estimates for exposure from drinking water are not of concern. All subpopulations had an exposure estimate that was less than 100% of the ADI.

7.1.4 Residential Risk

Risk estimates associated with residential application and postapplication exposure are not of concern.

7.1.5 Aggregate Risk

An aggregate acute risk was not required as there are no acute toxic endpoints of concern. Aggregate (drinking water and residential) short-term risk was not of concern. All subpopulations had an ARI that was greater than one.

7.2 Environmental Risk

Dithiopyr absorbs very strongly to soil and particles; therefore, it is persistent in most soils and water/sediment systems. There is also a potential that dithiopyr may appear in surface water through runoff. The risk assessment of dithiopyr indicates that adverse effects on non-target terrestrial and aquatic organisms may occur. To reduce the effects of dithiopyr in the environment, mitigation in the form of precautionary label statements and buffer zones are required.

7.3 Value

From the value perspective, dithiopyr is acceptable for continued registration.

8.0 Proposed Regulatory Decision

The PMRA is proposing continued registration of products containing dithiopyr for sale and use in Canada provided new risk-reduction measures are adopted.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that the drinking water risks, worker and non-occupational risks during mixing, loading, application and after dithiopyr is applied are acceptable, provided that the mitigation measures listed in Appendix X are implemented.

8.1.1.1 Proposed Mitigation for Occupational Handlers

The following mitigation measures are required for all commercial class products containing dithiopyr.

- Only one application is permitted per season
- An REI of 12 hours for all crops except golf courses
- The REI for golf courses: Do not re-enter until spray has dried

8.1.1.2 Proposed Mitigation for Non-Occupational Handlers

All domestic class granular-fertilizer products containing dithiopyr must also be limited to one application per season.

8.1.2 Proposed Regulatory Action Related to Environment

The risk assessment has indicated that adverse effects on non-target terrestrial plants and aquatic organisms are expected. To reduce the effects of dithiopyr in the environment, mitigation in the form of precautionary label statements and buffer zones are required. Environmental mitigation statements are listed in Appendix X.

8.1.3 Proposed Regulatory Action Related to Value

At this time, no regulatory action is proposed for dithiopyr as a consequence of the value assessment.

8.2 Additional Data Requirements

No additional data are required for dithiopyr at this time.

List of Abbreviations

↑	increase
↓	decrease
♂	male
♀	female
^{14}C	carbon 14
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
amu	atomic mass unit(s)
ARI	aggregate risk index
ASAE	American Society of Agricultural Engineers
ATPD	area treated per day
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
bwg	body-weight gain
°C	degree(s) Celsius
cm	centimetre(s)
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary cells
d	day(s)
DACO	data code
DNA	deoxyribonucleic acid
EC	emulsifiable concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental exposure concentration
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FC	food consumption
g	gram(s)
GD	gestation day
GI	gastrointestinal
GIT	gastrointestinal track
GOT	glutamate oxaloacetate transaminase
GPT	glutamic-pyruvic transaminase
ha	hectare(s)
HC_5	hazard concentration to 5%
HCT	hematocrit
HGB	hemoglobin
hr(s)	hour(s)

HGPRT	hypoxanthine-guanine phosphoribosyl transferase
i.p.	intraperitoneal
i.v.	intravenous
IUPAC	International Union of Pure and Applied Chemistry
K^+	potassium
K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LEACHM	Leaching Estimation and Chemistry Model
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
m	metre(s)
m^2	metre(s) square
m^3	metre(s) cube
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
mg	milligram(s)
M/L/A	mixers/loaders/applicators
mL	millilitre(s)
min	minutes
MOE	margin of exposure
mPa	milliPascal(s)
N/A	not applicable
NAWQA	National Water Quality Assessment (Program)
ng	nanogram(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NZW	New Zealand White
OC	organic carbon
OM	organic matter
ORETF	Outdoor Residential Exposure Task Force
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
PRZM/EXAMS	Pesticide Root Zone Model/Exposure Analysis Modelling System
RBC	red blood cells
REI	restricted-entry interval
RQ	risk quotient
S9	mammalian metabolic activation system

SD	Sprague Dawley
STORET	Storage and Retrieval Database
SSD	sensitivity species distribution
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
TTR	turf transferable residues
µg	microgram(s)
UDS	unscheduled DNA synthesis
USEPA	United States Environmental Protection Agency
UV	ultraviolet
wk	week
wt(s)	weight(s)

Appendix I Registered Dithiopyr Products as of 11 January 2008

Registration Number	Marketing Class	Registrant	Product Name	Formulation	Guarantee
23003	Commercial	Dow AgroSciences Canada Inc.	Dimension Turf Herbicide	Emulsifiable concentrate or emulsion	124 g/L
23585	Manufacturing Concentrate		Dithiopyr Manufacturing Concentrate Herbicide	Emulsifiable concentrate or emulsion	11%
23002	Technical		Dimension Technical Grade Herbicide	Solid	93.6%

Appendix II Registered Uses of Dithiopyr as of 11 January 2008

Only one end-use product is currently registered (Dimension Turf Herbicide—dithiopyr at 124 g/L; Registration Number 23003).[1] The formulation of this end-use product is emulsifiable concentrate or emulsion. Application is made once per year by ground equipment only.[2] No aerial application is allowed for any uses.

Use Site Category	Site	Weeds	Application Timing	Maximum Application Rate g a.i./ha)	Supported Uses
30 Turf	Turf (established turf grass including creeping bentgrass[3], Kentucky bluegrass, fine fescue[4], tall fescue, and perennial ryegrass)	Smooth crabgrass Large crabgrass	Pre-emergence	434 g a.i./ha (= 4.34 g/100 m^2)	Yes
			Postemergence	558 g a.i./ha (= 5.58 g/100 m^2)	

1 Pre-emergent control (liquid): 4.2 g of dithiopyr / 100 m^2 which is equivalent to 420 g a.i./ha.
Postemergent control (liquid): 4.2–5.4 g of dithiopyr /100 m^2 which is equivalent to 420–540 g a.i./ha.
Pre-emergent control (granular): 2.8–4.2 g of dithiopyr /100 m^2 which is equivalent to 280–420 g a.i./ha.
Postemergent control (granular): 4.2 g of dithiopyr /100 m^2 which is equivalent to 420 g a.i./ha.

2 The number of applications per year is not currently stated on the product label. The registrant proposes a maximum of one application per year as a risk mitigation measure.

3 Use of this product on certain older varieties of creeping bentgrass, such as "Cohansey" and "Seaside", will result in undesirable turf grass injury. **DO NOT** apply this product to Colonial bentgrass varieties.

4 Use of this product on certain varieties of Chewings fine fescue may result in undesirable turf injury. The following fine fescue varieties have been found to be sensitive to this product: Atlanta, Banner, Beauty, Bilgart, CF-2, Enjoy, HF-93. Highlight, Ivalo, Jamestown, Koket, Majenta, Mary, Pennlawn, Tamara, Tatjana, Waldorf and Waldina. Not all varieties of fine fescue have been tested.

Appendix III Toxology Assessment for Dithiopyr Technical

Table 1 Toxicology Profile for Dithiopyr

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption, Distribution, Metabolism and Excretion, Fischer Rats (5/sex/group)	• Single i.v. dose of 5 mg/kg bw • 99% purity		**Absorption**: ***Males:*** peak blood concentration reached 15 min. postdosing; ***Females:*** peak blood concentration reached 5 min. postdosing. Note: Females had a shorter elimination rate and distribution ½-life but a greater area under the curve (AUC). **Distribution:** ***Males:*** at 4, 8, 24 and 72 hrs postdosing, the highest percent activity was found in the gastrointestinal tract (GIT). By 168 hrs, the highest percent radioactivity was found in the fat (1.9%). ***Females:*** at 4, 8, 24, 72 and 168 hrs postdosing, the highest percent activity was found in the fat (7.2% at 168 hrs). **Metabolism:** Main urinary metabolites detected from 4–144 hrs: ***Males:*** U-1 (17.9%), U-2 (2.2%); ***Females:*** U-7 (19.2%), U-1 (7.0%), U-8 (3.5%). Main fecal metabolites in aqueous fraction from 24–268 hrs: ***Males:*** F-1 (16.2%), F-8 (8.5%), F-6 (3.6%); ***Females:*** F-1 (10.2%), F-6 (5.9%), F-8 (3.9%). Main fecal metabolites in organic fraction from 12–168 hrs: ***Males:*** F-6 (3%), F-10 (1.5%); ***Females:*** F-10 (3%), F-1 (1.5%). **Excretion:** ***Males:*** excreted a total of 36% and 64% of the dose in urine and feces, respectively. 168 hrs postdosing; ***Females:*** excreted a total of 48% and 45% of the dose in urine and feces, respectively. 168 hrs postdosing. Note: The majority of radioactivity was eliminated 72 hrs postdosing (in both genders). Note: The ½-lives of elimination were 21.3 (♂) and 33.2 (♀) hrs.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Absorption, Distribution and Excretion, Fischer Rats (5/sex/group)	• Single oral dose of 1, 5, 100 or 1000 mg/kg (by gavage) • 99% purity		**1, 5, 100 or 1000 mg/kg bw** **Absorption:** peak blood concentration reached 4–12 hrs postdosing. Note: Minimal sex or dose difference w/ ♀s having a shorter blood elimination rate and distribution ½-life but a greater AUC. **Distribution:** **5 mg/kg bw:** at 4, 8, 24 and 72 hrs postdosing, the highest percent activity was found in the GIT. By 168 hrs, the highest percent radioactivity was found in the fat (0.6% in ♂s, 3.3% in ♀s). **1000 mg/kg bw:** at 4, 8 and 24 hrs postdosing, the highest percent activity was found in the GIT. At 72 and 168 hrs postdosing, the highest percent radioactivity was found in the fat (6.4 and 0.6% at 72 and 168 hrs in ♂s, resp.; 7.1% and 1.5% at 72 and 168 hrs in ♀s, respectively.). **Metabolism:** **5 mg/kg bw:** Main urinary metabolites detected from 4–96 hrs: ***Males:*** U-1 (8.3%), U-3 (3.0%), U-7 (1.9%); ***Females:*** U-7 (18.8%), U-1 (4.8%), U-8 (2.3%). Main fecal metabolites in aqueous fraction from 12–144 hrs: ***Males:*** F-1 (8.9%), F-8 (6.0%), F-6 (2.6%); ***Females:*** F-1 (9.5%), F-6 (3.9%), F-8 (1.5%). Main fecal metabolites in organic fraction from 12–144 hrs: ***Males:*** F-10 (15.8%), F-6 (3.9%); ***Females:*** F-10 (3.9%), F-1 (0.9%). **1000 mg/kg bw:** Main urinary metabolites detected from 8–96 hrs: ***Males:*** U-7 (7.2%), U-1 (2.1%); ***Females:*** U-7 (16.2%), U-1 (3.5%), U-6 (2.8%). Main fecal metabolites in aqueous fraction from 4–120 hrs: ***Males:*** F-1 (8.3%), F-6 (3.0%), F-8 (2.3%); ***Females:*** F-1 (10.7%), F-6 (3.2%), F-5 (2.1%). Main fecal metabolites in organic fraction from 4–120 hrs: ***Males:*** F-10 (44.5%), F-6 (4.1%); ***Females:*** F-10 (31.8%), F-6 (2.7%).

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			Excretion: Note: There was a dose-response in elimination ½-life with a ½-life of 42 hrs at 1 mg/kg bw/day and 22–24 hrs at 1000 mg/kg bw/day. **5 mg/kg bw:** ***Males:*** excreted a total of 33% and 64% of the dose in urine and feces, respectively. 168 hrs postdosing; ***Females:*** excreted a total of 46% of the dose in both urine and feces, 168 hrs postdosing. Note: The majority of radioactivity was eliminated 96 hrs postdosing (in both genders). Note: The ½-lives of elimination were 17.9 (♂) and 24.3 (♀) hrs. Note: No to minimal radioactivity was eliminated in expired air. **1000 mg/kg bw:** ***Males:*** excreted a total of 20% and 70% of the dose in urine and feces, respectively. 168 hrs postdosing; ***Females:*** excreted a total of 32% and 66% of the dose in urine and feces, respectively. 168 hrs postdosing. Note: The majority of radioactivity was eliminated 96 hrs postdosing (in both genders). Note: The ½-lives of elimination were 18 (♂) and 21.6 (♀) hrs. Note: No to minimal radioactivity was eliminated in expired air.
Absorption, Distribution, Metabolism and Excretion, Fischer Rats (5/sex/group)	• Multiple oral doses of 5 mg/kg/day for 14 consecutive days (by gavage) • 99% purity		**Absorption:** Increasing radioactivity noted in blood w/maximum level on day 14. ***Males:*** peak blood concentration reached at 2–4 hrs after the last dose; ***Females:*** peak blood concentration reached at 8 hrs after the last dose. Note: There were comparable blood elimination ½-lives between sexes but these were much shorter than single dose blood elimination ½-lives, ♀s had a greater AUC. **Distribution:** ***Males:*** 4 and 24 hrs following the last dose, the highest % activity (as % of the last dose or total dose) was in the GIT. 168 hrs following the last dose, the highest % activity (as % of the last dose or total dose) was in fat (3.4% of last dose). ***Females:*** 4 hrs following the last dose, the highest % activity (as % of the last dose or total dose) was in the GIT. 24 and 168 hrs following the last dose, the highest % activity (as % of the last dose or total dose) was in fat (30.0% and 7.4% of last

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			dose at 24 and 168 hrs, respectively.). **Metabolism:** Main urinary metabolites detected from 4–120 hrs: ***Males:*** U-1 (23.5%), U-2 (2.1%); ***Females:*** U-7 (13.2%), U-1 (8.8%). Main fecal metabolites in aqueous fraction from 4–168 hrs: ***Males:*** F-1 (13.8%), F-6 (8.0%); ***Females:*** F-1 (7.7%), F-8 (4.2%), F-6 (3.3%). Main fecal metabolites in organic fraction from 4–168 hrs: ***Males:*** F-6 (6.1%), F-10 (3.1%); ***Females:*** F-6 (6.7%), F-10 (6.5%). **Excretion:** ***Males:*** an average daily excretion of 31% and 52% in urine and feces, respectively was noted; ***Females:*** an average daily excretion of 41% and 43% in urine and feces, respectively was noted. Note: The majority of radioactivity was eliminated 96 hrs following the last dose (in both genders).

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism and Excretion Studies, Rhesus Monkeys (3 ♂/group)	• Single i.v. dose of 0.01 or 5 mg/kg bw • 98–99.5% purity		**Metabolism**: Metabolite mixtures in both urine and feces for both dose groups were found to consist of ≤1% of parent, 1 major metabolite (dicarbothioic acid) and lesser amounts of other metabolites (diacid, monoacid 2 and several peptide conjugates). Virtually all the parent compound was rapidly and extensively metabolized. **Excretion**: *essentially all of the administered radiolabel was recovered in the urine and feces within 2–3 days after dosing.* 0.01 mg/kg bw: within 72 hrs of dosing, 56% and 30% of the administered dose was excreted in the urine and feces, respectively. Urine was the major route of excretion with approximately 58.5% of the administered dose and the remaining dose excreted in the feces; 5 mg/kg bw: within 72 hrs of dosing, 65% and 29% of the administered dose was excreted in the urine and feces, respectively. Urine was the major route of excretion with approximately 68.0% of the administered dose and the remaining dose excreted in the feces.
Metabolism and Excretion Studies, Dermal-Rhesus Monkeys (3 ♂/group)	• Single 12-hrs dermal application of 4 or 40 mg/kg bw • 98.8–99.5% purity		**Metabolism**: The parent compound was rapidly and extensively metabolized. The metabolite mixture in the urine and feces for both dose groups contained ≤3% parent, 1 major metabolite (dicarbothioic acid) and lesser amounts of other metabolites (diacid, monoacid 2 and several peptide conjugates). **Excretion**: *urine was the primary route of excretion for both the low- and high-dose groups.* 4 mg/kg bw: ~0.17% of the dose was excreted in the urine and 0.05% was excreted in the feces; 40 mg/kg bw: ~0.04% of the dose was excreted in the urine and 0.02% was excreted in the feces.
Acute Toxicity Studies			
Acute Oral – ICR Mice (10/sex/group)	• 2500 or 5000 mg/kg bw • 90.9% purity		LD_{50} > 5000 mg/kg bw Low Toxicity.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Acute Oral – SD Rats (10/sex/group)	• 2500 or 5000 mg/kg bw • 90.9% purity	LD_{50} > 5000 mg/kg bw Low Toxicity.	
Acute Dermal – SD Rats (10/sex/group)	• 1000 or 5000 mg/kg bw • 90.9% purity	LD_{50} > 5000 mg/kg bw Low Toxicity.	
Acute Inhalation – Fischer 344 Rats (10/sex/group)	• 0 or 5.98 mg/L, aerosol, nose-only exposure • 99.0% purity	LC_{50} > 5.98 mg/l Low Toxicity.	
Eye Irritation – NZW Rabbits (2♂ and 4♀)	• 0.1 mL/eye • 91.5% purity	Slight Eye Irritant.	
Dermal Irritation – NZW Rabbits (2♂ and 4♀)	• 0.5 g/test site • 91.5% purity	Non-Irritating.	
Dermal Sensitization – Hartley Albino Guinea Pigs (5/sex)	• 100% used for induction and challenge • 91.5% purity	**Not a dermal sensitizer** in Buehler assay.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Subchronic Toxicity Studies			
13-week Dietary Toxicity – ICR Mice (12/sex/group)	• 0, 10, 100, 1000 or 5000 ppm (= 0, 1.2/1.5, 11.8/14.2, 116/153 or 611/813 mg/kg bw/day in ♂/♀) for 13 wks • 91.6% purity	11.8(♂)/ 14.2(♀)	***Males:*** ≥11.8 mg/kg bw/day: dark-coloured liver and diffuse hepatocellular swelling (*non-adverse*); ≥116 mg/kg bw/day: ↑ ALP, GOT, GPT and BUN, ↑ absolute and relative liver wts, liver alterations (diffuse hepatocellular swelling, hepatocellular vacuolation); 611 mg/kg bw/day: ↓ bwg and food efficiency, ↓ urinary protein level, Hgb, MCH, glucose and specific gravity of urine, ↑ total protein and Ca^{+2}, ↑ rel. adrenal wt, liver alterations (dissociation of hepatocellular cords, single-cell necrosis of hepatocytes, brown pigment deposition of kupffer's cells, bile duct proliferation), acidophilia of proximal tubular cells of kidneys, cortical hypertrophy of adrenals. ***Females:*** ≥14.2 mg/kg bw/day: dark-coloured liver and diffuse hepatocellular swelling (*non-adverse*); ≥153 mg/kg bw/day: ↑ ALP, GOT, GPT and BUN; ↓ glucose, ↑ abs. and rel. liver wt and rel. kidney wt, diffuse hepatocellular swelling, acidophilia of proximal tubular cells of kidneys, focal necrosis of hepatocytes; 813 mg/kg bw/day: ↓ bwg and food efficiency, ↓ Hct, Hgb, MCH and specific gravity of urine, ↑ total protein, total cholesterol and Ca^{+2}, ↓ rel. ovary wt and ↓ abs. brain wt, liver alterations (hepatocellular vacuolation, dissociation of hepatocellular cords, brown pigment deposition of kupffer's cells, bile duct proliferation, single-cell necrosis of hepatocytes), brown pigment deposition in cortico-medullary junction of adrenals, ovarian atrophy.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
13-week Dietary Toxicity – Fischer 344 Rats (12/sex/group)	• 0, 10, 100, 1000 or 5000 ppm (=0, 0.6/0.7, 6.0/6.6, 60.6/67.0 or 362/379 mg/kg bw/day in ♂/♀) for 13 wks • 91.3% purity	6.0(♂)/0.7(♀)	***Males:*** ≥60.6 mg/kg bw/day: ↓ Hct and Hgb, ↑ albumin, total cholesterol and urinary specific gravity, ↑ abs. and rel. liver and thyroid wts and rel. kidney wt, hyaline cast in kidney, follicular cell hypertrophy of thyroid, diffuse hepatocellular swelling; 362 mg/kg bw/day: ↓ bwg, FC and food efficiency, ↓ RBC, total glucose, globulin, creatinine, Na^+, triglyceride, MCH and MCV, ↑ ALP, γ-GTP, BUN, K^+, phosphorus, total bilirubin, albumin to globulin ratio and urinary protein, ↑ rel. brain, heart, pituitary and testes wts, ↓ abs. brain, heart, thymus, spleen and pituitary wts, cortical cell hypertrophy of Zona Glomerulosa and Fasciculata in adrenal, foam cell aggregation of lung. ***Females:*** ≥6.6 mg/kg bw/day: ↑ total cholesterol and protein, ↑ abs. and rel. liver wt and abs. kidney and adrenal wts, diffuse hepatocellular swelling; ≥67.0 mg/kg bw/day: ↓ MCH, ↑ urinary specific gravity, ↑ rel. kidney wt and abs. thyroid wt, focal tubular atrophy in kidney, follicular cell hypertrophy of thyroid, cortical cell hypertrophy of Zona Fasciculata in adrenal, ↑ abs. brain and heart wts; 379 mg/kg bw/day: ↓ bwg, Hct, Hgb, MCV, creatinine, triglyceride and food efficiency, ↑ FC, ALP, γ-GTP, albumin, albumin to globulin ratio, glucose, BUN, Ca^{+2} and urinary protein, ↓ abs. and rel. spleen wt and abs. thymus wt, ↑ rel. heart, brain, thyroid and adrenal wts, hyaline cast of kidney, cortical cell hypertrophy of Zona Glomerulosa in adrenal, bile duct proliferation.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
13-week Oral Toxicity – Beagle Dogs (6/sex/group)	• 0, 1, 10 or 30 mg/kg bw/day by capsule • 90.6% purity	1	***Males:*** ≥10 mg/kg bw/day: distended gallbladder, brown pigment deposition in Kupffer cells and in bile canaliculi; 30 mg/kg bw/day: ↑ vomiting, ALP, GOT and γ-GPT, ↓ albumin and total cholesterol, dark-coloured livers, ↑ abs. and rel. liver wts, mononuclear cell infiltration. ***Females:*** ≥10 mg/kg bw/day: dark-coloured liver, brown pigment deposition in Kupffer cells and in bile canaliculi, mononuclear cell infiltration; 30 mg/kg bw/day: ↑ ALP and GOT (transient), ↓ albumin and Ca^{+2}, distended gallbladder w/sandy texture, ↑ abs. and rel. liver wts and ↑ rel. kidney wt.
21-Day Dermal Toxicity – Sprague Dawley Rats (5/sex/group)	• 0, 50, 500 or 1000 mg/kg bw/day • 92.2% purity	1000	≥50 mg/kg bw/day: very slight erythema (treated skin) (♀) (*non-adverse*); ≥500 mg/kg bw/day: very slight erythema (treated skin) (♂) (*non-adverse*); 1000 mg/kg bw/day: ↑ abs. and rel. liver wts (*non-adverse*).
Chronic Toxicity/Oncogenicity Studies			
12-Month Oral Toxicity – Beagle Dogs (6/sex/group)	• 0, 0.5, 5.0 or 25.0 mg/kg bw/day (by capsule) • 94.5% purity	5	***Males:*** ≥5.0 mg/kg bw/day: ↑ K^+, brown pigment deposition in liver (*non-adverse*); 25.0 mg/kg bw/day: ↑ platelet count and ALP, ↓ glucose (transient) and chloride, dark-coloured liver, distended and blackish-sandy material in gallbladder, ↑ abs. and rel. liver wts, liver alterations (single-cell necrosis of hepatocytes, fibrosis, bile duct proliferation, pseudo-bile ductular formation of liver), ↑ mucoidal secretion of gallbladder, brown pigment deposition in proximal tubular cells of kidney.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			Females: ≥5.0 mg/kg bw/day: brown pigment deposition in liver, dark-coloured liver (*non-adverse*); 25.0 mg/kg bw/day: ↑ vomiting (transient) and ALP, ↓ albumin (transient) and K^+, ↑ abs. and rel. liver wts and rel. kidney wt, distended gallbladder, liver alterations (enlarged, fibrosis, pseudo-bile ductular formation, bile ductular proliferation and single-cell necrosis of hepatocytes), brown pigment deposition in proximal tubular cells of kidney.
18-Month Dietary Carcinogenicity – ICR Mice (70/sex/group, w/ 10/sex/group for interim sacrifice at 13 and 52 wks)	• 0, 3, 30 or 300 ppm (= 0, 0.3/0.4, 3.3/3.8 or 32.2/ 38.4 mg/kg bw/day in ♂/♀) for 78 weeks • 91.5% purity	3.3(♂)/3.8(♀)	***Males:*** 3.3 mg/kg bw/day: ↑ rel. liver wt (transient) (*non-adverse*); 32.2 mg/kg bw/day: ↑ abs. and rel. liver wts, liver alterations (enlarged and dark coloured, diffuse hepatocellular swelling, ↑ brown pigment deposition in hepatic, kupffer cells and bile canaliculi, bile duct proliferation), ↑ extramedullary hematopoiesis of spleen, cortical cell swelling of adrenals. ***Females:*** 3.8 mg/kg bw/day: ↑ rel. liver wt (transient) (*non-adverse*); 38.4 mg/kg bw/day: ↑ abs. and rel. liver and adrenal wts and abs. brain wt, liver alterations (enlarged and dark coloured, centrilobular and diffuse hepatocellular swelling, ↑ brown pigment deposition in hepatic cells and kupffer cells), ↑ brown pigment deposition in cortical-medullary junction of adrenals. **No evidence of carcinogenicity**.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
24-Month Dietary Carcinogenicity – Fischer 344 Rats (90/sex/group, w/ 10/sex/group for interim sacrifice at 13, 26, 52 and 78 wks)	• 0, 3, 10, 100 or 300 ppm (= 0, 0.1/0.1, 0.4/0.4, 3.6/4.3 or 11.1/13.2 mg/kg bw/day in ♂/♀) for 104 weeks • 93.7% purity	0.4	***Males:*** ≥3.6 mg/kg bw/day: ↑ rel. liver and kidney wt (transient), spongiosis hepatis of liver, chronic nephropathy of kidney; 11.1 mg/kg bw/day: ↑ albumin, total protein, total cholesterol, glucose and Ca^{+2}, transient ↑ in albumin to globulin ratio, BUN, ALP and GPT, transient ↓ in Na^{+} and triglyceride, ↑ abs. and rel. liver and kidney wts and rel. adrenal wt, liver alterations (enlarged and dark coloured, focal hepatocellular necrosis), coarse surface of the kidney. ***Females:*** ≥4.3 mg/kg bw/day: transient ↑ in albumin, total cholesterol, total protein and GPT, ↑ phosphorus, bile ductal proliferation of liver, early change of chronic nephropathy of kidney (transient); 13.2 mg/kg bw/day: transient ↑ in albumin to globulin ratio, BUN and GOT, ↑ Ca^{+2}, transient ↓ALP and triglyceride, ↑ abs. and rel. liver weights and abs. kidney, thyroid and brain wt and rel. kidney wt, liver alterations (enlarged, coarse surface), chronic nephropathy of kidney. **No evidence of carcinogenicity**.
Developmental/Reproductive Toxicity Studies			
Teratogenicity, Oral-Sprague Dawley Rats (24♀/group)	• 0, 30, 300 or 1000 mg/kg bw/day on GD 6–15 (by gavage) • 91.3 % purity	Maternal = 300 Developmental = 1000	**Maternal**: 1000 mg/kg bw/day: ↓ mean bwg (transient) and mean daily FC. **Developmental**: No effects noted. **No evidence of teratogenicity.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Teratogenicity, Rabbits (18♀/group)	• 0, 150, 500 or 1000 mg/kg bw/day on GD 7–19 (by gavage) • 93 % purity	Maternal = 500 Developmental = 1000	**Maternal**: 1000 mg/kg bw/day: ↓ bwg (transient). **Developmental**: No effects noted. **No evidence of teratogenicity.**
Reproduction, Dietary-Sprague Dawley Rats (24/sex/group) (2-generation)	• 0, 25, 250 or 2,500 ppm (=0, 1.7/1.9, 16.4/18.6 or 170/187 mg/kg bw/day F_0 ♂/♀; 0, 2.0/2.3, 19.9/22.5 or 218/230 mg/kg bw/day F_1 ♂/♀) • 93.7% purity	Parental = 1.9 (F_0)/ 2.0 (F_1) Reproductive = 1.9 Offspring = 1.9	**Parental**: **F_0 *Males:*** ≥16.4 mg/kg bw/day: ↑ rel. liver wt (*non-adverse*); 170 mg/kg bw/day: ↓ bw and abs. spleen wt, ↑ abs. liver and kidney wts and rel. brain and testes wts, liver alterations (enlarged, dark, bile stasis, focal hepatocellular necrosis, diffuse hepatocellular swelling), focal tubular atrophy of kidney, follicular cell hypertrophy of thyroid, cortical cell hypertrophy of adrenals. **F_0 *Females:*** ≥18.6 mg/kg bw/day: ↑ abs. kidney wts, cortical cell hypertrophy in adrenals; 187 mg/kg bw/day: enlarged and dark liver, ↑ rel. kidney wt and abs. and rel. liver wt, focal tubular atrophy of kidney, follicular cell hypertrophy of thyroid, diffuse hepatocellular swelling. **F_1 *Males:*** ≥19.9 mg/kg bw/day: transient ↓ in bw and FC; 218 mg/kg bw/day: ↑ abs. and rel. liver wts and rel. kidney, brain and testes wts, ↓ abs. adrenal wts, liver alterations (enlarged, dark, diffuse hepatocellular swelling, bile stasis), follicular cell hypertrophy of thyroid, cortical cell hypertrophy of adrenals. **F_1 *Females:*** ≥22.5 mg/kg bw/day: transient ↓ in bw and FC; 230 mg/kg bw/day: ↑ abs. and rel. liver wts, ↓ abs. spleen wt, liver alterations (enlarged, dark, diffuse hepatocellular swelling, bile stasis), focal tubular atrophy of kidney, follicular cell hypertrophy of thyroid, cortical cell hypertrophy of adrenals.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			Reproductive: **F_1 pups:** ≥16.4/18.6 mg/kg bw/day: ↓ birth weight (♂); 170/187 mg/kg bw/day: ↓ birth weight (♀). **F_2 pups:** 218/230 mg/kg bw/day: ↓ birth weight. **Offspring**: **F_1 weanlings:** ≥16.4/18.6 mg/kg bw/day: diffuse hepatocellular swelling; white spots on liver (♂); 170/187 mg/kg bw/day: ↓ bw, ↑ incidence of pups found dead, hyperthermia, debility, liver alterations (white spots, enlarged, bile stasis, fibrosis/mineralization, bile ductal proliferation, epithelial swelling of bile duct). **F_2 pups, lactation days 0–4:** ≥19.9/22.5 mg/kg bw/day: liver alterations (white spots, focal hepatocellular necrosis); 218/230 mg/kg bw/day: ↓ bw, liver alterations (enlarged, white spots, focal hepatocellular necrosis, fibrosis). **F_2 pups and weanlings autopsied during lactation days 5–27:** ≥19.9/22.5 mg/kg bw/day: liver alterations (white spots, diffuse hepatocellular swelling); 218/230 mg/kg bw/day: ↓ bw, liver alterations (enlarged, fibrosis, mineralization).
Genotoxicity Studies			
Ames Test – In vitro Reverse mutation • *Salmonella typhimurium*	• 10, 50, 100, 500, 1000 and 5000 µg/plate ± rat liver activation • 93.7% purity	**Negative**	
Ames Test – In vitro Reverse mutation • *Salmonella typhimurium*	• Initial and Repeat tests: 0.03, 0.10, 0.30, 1.04 and 3.11 mg/plate ± rat liver activation	**Negative**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
	• Retest results for TA100: 0.05, 0.10 and 0.15 mg/plate • 91.5% purity		

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
In vitro Gene Mutation Assay • CHO/HGPRT	• Preliminary test: 0, 0.3, 3.0, 10, 30, 70, 100, 300 and 1000 µg/mL ± rat liver activation • Confirmation test: 10, 30, 100, 200 and 300 µg/mL - activation; 3, 7, 10, 20 and 30 µg/mL + activation • 93.7% purity	**Negative**	
In vitro Cytogenetics Assay – Chromosomal Aberrations • Chinese hamster lung cell line	• 0.001, 0.00033, 0.0001, 0.000033 and 0.00001 M ± rat liver activation • 97.6% purity	**Negative**	
In vitro Unscheduled DNA Synthesis Studies • Primary Rat Hepatocyte Cultures	• 0.1 to 1000 µg/mL • 93.7% purity	**Negative**	
Other Studies			
Pharmacology and Behavioural Study, Intraperitoneal (i.p.) – Mice (3/sex/group)	• single i.p. dose of 0, 19.5, 78.1, 313, 1250 or 5000 mg/kg bw • 93.7% purity		≥313 mg/kg bw: ↓ spontaneous activity, body and abdominal tones, respiratory rate, hypothermia and narrowed palpebral opening, clearing by postdosing day 4; 5000 mg/kg bw: 2 ♂s died on postdosing days 2 and 3, ↑ incidence of passiveness, righting reflex and piloerection, clearing by postdosing day 4.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Pharmacology and Behavioural Study, Oral – Rabbits (3 ♂s/group)	• Single oral dose of 0, 313, 1250 or 5000 mg/kg • 93.7% purity	No abnormal behaviour was noted.	

Table 2 Toxicology Endpoints for Health Risk Assessment for Dithiopyr

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[a]
Acute Reference Dose	Not required			
Chronic Dietary	Altered liver pathology	An oral 2-year chronic dietary study in rats	0.4	100
	ADI = 0.004 mg/kg bw/day			
Short-Term Dermal	Residential and Occupational			
	No treatment related signs of systemic toxicity	A dermal 21-day toxicity study in rabbits	1000 (highest dose tested)	300
Intermediate-Term Dermal	Occupational			
	No treatment related signs of systemic toxicity	A dermal 21-day toxicity study in rabbits	1000 (highest dose tested)	1000
Short-Term and Intermediate-Term Inhalation	Residential and Occupational			
	Altered liver and kidney pathology	A dietary 13-week toxicity study in rats	0.7	100
Non-Dietary Short-Term Oral Ingestion	Altered liver pathology	A two-generation reproduction study in rats	1.9	100

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[a]
Aggregate Risk Assessment—Food, Drinking Water and Residential (dermal, inhalation and incidental oral)	Dermal component			
	No treatment related signs of systemic toxicity	A dermal 21-day toxicity study in rabbits	1000 (highest dose tested)	300
	Oral and Inhalation components			
	Altered liver and kidney pathology	A dietary 13-week toxicity study in rats	0.7	100

[a] Composite assessment factor (CAF) refers to total of uncertainty and *Pest Control Products Act* factors for dietary assessments, MOE refers to desired margin of exposure for occupational or residential assessments.

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

Appendix IV Occupational and Residential Exposure Risk Estimates for Dithiopyr

Table 1 M/L/A Short-Term to Intermediate-Term Occupational Mixer/Loader/Applicator Exposure and Risk Assessment

Scenario	Form	Application Equipment	Data Source	Rate kg a.i./ha	ATPD (ha)	kg a.i. Handled per Day	Unit Exposure (µg/kg a.i.)		Exposure (µg/kg/day)[a]		MOE[b]		ARI[c]
							Total		Daily		Dermal (Target = 300–1000)	Inhalation (Target = 100)	
							Dermal	Inhalation	Dermal	Inhalation			
Baseline PPE: long-sleeved shirt, long pants, chemical-resistant gloves (where applicable)[d]													
Residential Turf	EC	Backpack	PHED	0.558	0.4	0.22	5445.9	62.1	17.36	0.2	58 000	3500	49
		Turf Gun	Exposure Study[e]	1.12	N/A	1.87	N/A	N/A	0.216[f]		3200[g] (Target =100)		N/A
Golf Courses / Sod Farms	EC	Backpack	PHED	0.558	0.4	0.22	5445.9	62.1	17.36	0.2	58 000	3500	49
		Turf Gun	ORETF	0.558	2	1.12	785	4	12.52	0.06	80 000	11000	74
		Groundboom – golf course	PHED	0.558	16	8.93	83.63	2.56	10.67	0.33	94 000	2000	65
		Groundboom – sod farm	PHED	0.558	30	16.74	5445.9	62.1	20	0.61	50 000	1000	34

Form = formulation; EC = emulsifiable concentrate; ATPD = area treated per day; MOE = margin of exposure; ARI = aggregate risk index

[a] Where exposure (µg/kg/day) = (unit exposure × kg a.i. handled per day)/70 kg bw.

[b] MOE = NOAEL/exposure. Dermal MOE is based on a NOAEL of 1000 mg/kg/day from a 21-day dermal rabbit study; target MOE is 300 (short-term) or 1000 (intermediate-term). Inhalation MOE is based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE is 100.

[c] ARI is not of concern when greater than one. It was calculated using the following equation: ARI = 1/[(target MOE and dermal/MOE dermal) + (target MOE and inhalation/inhalation MOE)].

[d] From chemical-specific biomonitoring study.

[e] Maximum of all 18 workers sampled.

[f] MOE is based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE is 100.

[g] Gloves were not included in the groundboom application scenarios as the data quality was better for non-gloved scenarios than gloved scenarios.

Table 2 Dermal Occupational Postapplication Exposure and Risk Assessment

Activity	Form	Transfer Coefficient[a] (cm^2/hr)	Mean TTR[b] (µg/cm^2)	Dermal Exposure (µg/kg bw/day)	MOE[c] (day of application)	REI[d]
Workers in Golf Courses and Sod Farms			**Target: 1000**			
Transplanting, hand weeding, hand harvesting, mechanical harvest	EC	16500	0.01064	20.05	50 000	**12 hours**
Aerating, fertilizing, hand pruning, scouting, mechanical weeding, seeding, irrigation	EC	500	0.01064	0.61	1 650 000	**12 hours**

Form = formulation, EC = emulsifiable concentrate

[a] Transfer coefficients are from the Science Advisory Council for Exposure Agricultural Transfer Coefficient document

[b] TTR is the maximum liquid mean TTR value from all monitored activities in the submitted TTR study.

[c] MOE = NOAEL/exposure. Based on NOAEL of 1000 mg/kg bw/day from a 21-day dermal rabbit study; target MOE of 300.

[d] REI = Restricted-entry interval

Table 3 Inhalation and Aggregate Occupational Postapplication Exposure and Risk Assessment

Scenario	Cubic Rate[a] (µg/m^3)	Inhalation Rate[b] (m^3/hr)	Inhalation Exposure[c] (µg/kg bw/day)	Inhalation MOE[d] (Target = 100)	Dermal MOE[e] (Target = 300)	ARI[f]
Golf courses/ sod farms	7.82	1.6	1.43	490	50 000	4.5

[a] Maximum air concentration from the submitted volatility study.

[b] Moderate inhalation rate.

[c] Inhalation exposure is calculated by the following equation: Exposure = [cubic rate × inhalation rate × duration (8 hr)]/bw (70 kg).

[d] Inhalation MOE is based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE is 100.

[e] Dermal MOE is from Appendix IV, Table 2 and is based on a dermal NOAEL of 1000 mg/kg bw/day; target MOE is 300.

[f] ARI is not of concern when greater than one. It was calculated using the following equation: ARI = 1/[(target MOE dermal/MOE dermal) + (target MOE inhalation/inhalation MOE)].

Table 4 Short-Term Residential Applicator Exposure and Risk Assessment

Application Equipment[a]	Data Source[b]	Rate (g a.i./m²)	Area Treated Per Day (m²/day)[c]	Unit Exposure (µg/kg a.i. handled)		Dose[d] (µg/kg bw/day)		MOE[e, f]		ARI[g]
				Dermal	Inhalation	Dermal	Inhal	Dermal (Target= 300)	Inhal (Target=100)	
Granular Fertilizer Product to Residential Lawns										
Push Rotary Spreader	ORETF	0.042	2000	1378	1.72	1.65	0.0021	600 000	340 000	**513**
Belly grinder[f, h]	PHED	0.042	2000	252 838	126.9	303	0.152	3300	4600	**3.08**
Granules dispersed by hand[f]	PHED	0.042	10	172 895	126	1.04	0.0036	960 000	190 000	**642**

a Homeowner PPE consists of short-sleeved shirt, shorts, and no gloves.

b Median unit exposures are used from ORETF, best-fit unit exposures are used from PHED.

c From EPA standard operating procedures for Residential Exposure Assessments: 2000 m² for belly grinders and push spreaders. 10 m² for granules by hand.

d Where dose µg/kg bw/day = (unit exposure × area treated/day × use rate)/70 kg bw.

e MOE = NOAEL/exposure. Dermal MOE is based on a NOAEL of 1000 mg/kg bw/day from a 21-day dermal rabbit study; target MOE is 300. Inhalation MOE is based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE is 100.

f There were no data available for 'no glove' scenarios in PHED, so gloved scenarios were used as surrogate. These are considered to underestimate the exposure to homeowners, as homeowners are considered to not wear gloves.

g There is uncertainty with the belly grinder scenario as there was no adequate hand exposure data, so surrogate hand data (gloved) from the granular bait by hand scenario was used.

i ARI = aggregate risk index. Values greater than 1 are not of concern.

Table 5 Residential Postapplication Dermal Exposure and Risk Assessment

Activity	Formulation	Transfer Coefficient (cm^2/hr)	Mean TTR[a] ($\mu g/cm^2$)	Dermal Exposure[b] (µg/kg bw/day)	MOE[c] (Day 0)
Adults					**Target: 300**
Golfer	EC	500	0.01064	0.150	6 600 000
	Gran		0.000226	0.003	310 000 000
Postapplication turf activities[d]	EC	N/A		41.8	24 000
	Gran			1.33	750 000
Youth					**Target: 300**
Golfer	EC	500	0.01064	0.27	3 700 000
	Gran		0.000226	0.01	172 000 000
Postapplication turf activities[d]	EC	N/A		51.7	19 000
	Gran			1.65	610 000
Children					**Target: 300**
Postapplication turf activities[d]	EC	N/A		62.5	16 000
	Gran			1.99	500 000

EC = emulsifiable concentrate; Gran = granular fertilizer

[a] The highest liquid and granular mean TTR values from all monitored activities in the TTR study were used. The granular TTR was adjusted for the Canadian application rate.

[b] Exposure was calculated for golfers using the following equation: Exposure = [TTR × TC × Duration (4 hours for golfers)]/bw (70 kg for adults, 39 kg for youth). For turf activities, exposure is from the postapplication passive dosimetry exposure study. For children and youth, the exposure value was scaled for surface area and body weight.

[c] MOE = NOAEL/exposure. Based on NOAEL of 1000 mg/kg bw/day from a 21-day dermal rabbit study; target MOE of 300.

[d] Shorts and short-sleeved shirts were assumed to be worn for residential postapplication exposure scenarios.

Table 6 Residential Postapplication Inhalation Exposure and Risk Assessment

Scenario	Average Air Concentration[a] (µg/m³)	Inhalation Rate[b] (m³/hr)	Inhalation Exposure[c] (µg/kg bw/day)	Inhalation MOE[d]
Granular Formulation				**Target: 100**
Adult (70 kg)	1.37	1	0.0391	**18 000**
Youth (39 kg)		1	0.0702	**10 000**
Children (15 kg)		0.7	0.128	**5500**

[a] 30-day average air concentration from the turf volatility study, from the air pumps found in the centre of the plot at the height of 30 cm above ground.
[b] Default inhalation rates.
[c] Inhalation exposure = [concentration in air × inhalation rate × exposure time (2 hrs)] or bw.
[d] MOE = NOAEL/exposure. Based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE of 100.

Table 7 Residential Postapplication Aggregate Exposure and Risk Assessment

Activity	Formulation	Dermal MOE[a]	Inhalation MOE[b]	Oral MOE [c]			ARI[g]
				Hand-to-Mouth [d]	Object-to-Mouth[e]	Ing. of Soil[f]	
Adults (70 kg)							
Golfer	EC	6 600 000	18 000	N/A	N/A	N/A	178
	Gran	31 000 000					179
Postapplication Turf Activities	EC	13 000					55
	Gran	57 000					167
Youth (39 kg)							
Golfer	EC	3 700 000	10 000	N/A	N/A	N/A	99
	Gran	17 000 000					100
Postapplication Turf Activities	EC	7300					39
	Gran	32 000					95
Children (15 kg)							
Postapplication Turf Activities[de]	EC	8900	5500	840	6700	76 000	3.3
	Gran	380 000		1100	8700	100 000	4.4

EC = emulsifiable concentrate; Gran = granular fertilizer; Ing. = ingestion

[a] Dermal MOEs are from Appendix IV, Table 5. Based on a NOAEL is 1000 mg/kg bw/day from a 21-day dermal rabbit study; target MOE of 300.

[b] Inhalation MOEs are from Appendix IV, Table 6. Based on a NOAEL of 0.7 mg/kg bw/day from a 13-week dietary study in rats; target MOE of 100.

[c] Non-dietary short-term oral MOE is based on a NOAEL of 1.9 mg/kg bw/day from an oral rat reproduction study; target MOE of 100.

[d] Hand-to-mouth exposure was based on the following equation: Exposure = [DFR (0.085 and 0.065 $\mu g/cm^2$ for liquid and granular formulations, respectively) × surface area (20 cm^2) × # of events/hr (20) × duration (2 hrs) × saliva extraction factor (50%)] / body weight (15 kg).

[e] Object-to-mouth exposure was based on the following equation: exposure = [DFR (0.341 and 0.261 $\mu g/cm^2$ for liquid and granular formulations, respectively) × object area (25 cm^2) × saliva excretion factor (50%)]/ body weight (15 kg).

[f] Ingestion of soil exposure was based on the following equation: Exposure = (application rate (5.58 and 4.2 $\mu g/cm^2$ for liquid and granular formulations, respectively) × ingestion rate (0.1 g) × fraction available in the top 1 cm of soil (100%) × 0.67)/body weight (15 kg).

[g] ARI is not of concern when greater than one. It was calculated using the following equation: ARI = 1/[(target MOE dermal/MOE dermal) + (target MOE inhalation/inhalation MOE) + (target MOE oral/ hand-to-mouth MOE) + (target MOE oral/ object-to-mouth MOE) (target MOE oral/ ingestion of soil MOE)].

Appendix V Drinking Water Exposure and Risk Estimates for Dithiopyr

Table 1 Chronic Drinking Water Exposure and Risk Estimates for Dithiopyr By Population Subgroup

Population Subgroup	Total Exposure	
	mg/kg bw/day	% of Acceptable Daily Intake[a]
General Population (total)	0.000259	6.5%
Infants (<1 year)	0.00085	21.2%
Non-nursing infants	0.000315	7.9%
Children 1 to 6 years	0.000362	9.1%
Children 7 to 12 years	0.000235	5.9%
Females 13 to 19 (not pregnant or nursing)	0.000182	4.6%
Females 20+ (not pregnant or nursing)	0.000259	6.5%
Males 13 to 19 years	0.000191	4.8%
Males 20+ years	0.000232	5.8%
Seniors 55+ years	0.000255	6.4%
Children 1 to 2 years	0.000385	9.6%
Children 3 to 5 years	0.00036	9.0%
Children 6 to 12 years	0.000249	6.2%
Youth 13 to 19 years	0.000187	4.7%
Adults 20 to 49 years	0.000242	6.1%
Adults 50+ years	0.000255	6.4%
Females 13 to 49 years	0.000241	6.0%

Bolded values were used in the aggregate risk assessment. Aggregate risk assessment is shown in Appendix VI.

[a] ADI = 0.004 mg/kg bw/day

Appendix VI Aggregate Exposure and Risk Assessment for Dithiopyr

Table 1 Short-Term Aggregate Exposure and Risk Assessment for Dithiopyr

Scenario	Drinking Water Exposure[a] (µg/kg bw/day)	Homeowners Applicator Exposure[a] (µg/kg bw/day)		Exposure from Re-entering Treated Turf[a] (µg/kg bw/day)			MOE[b]		ARI[c]
		Dermal	Inhalation	Dermal	Inhalation	Oral	Dermal	Inhalation/Oral	
Granular Products									
Adults (70 kg)									
Push Rotary Spreader	0.26	1.65	0.0021	1.76	0.223	N/A	290 000	2330	23
Belly Grinder		303	0.152	1.76	0.223	N/A	3300	1550	7
Granular Bait by Hand		1.04	0.0036	1.76	0.223	N/A	360 000	2320	23
Golfer		N/A	N/A	0.003	0.223	N/A	3×10^5	2350	23
Postapplication Turf Activities		N/A	N/A	1.76	0.223	N/A	570 000	2350	23
Youth (39 kg)									
Postapplication Turf Activities	0.19	N/A	N/A	3.15	0.4	N/A	320 000	2720	27
Golfer		N/A	N/A	0.01	0.4	N/A	2×10^5	2720	27
Children (15 kg)									
Postapplication Turf Activities	0.85	N/A	N/A	2.63	0.73	1.97	380 000	240	2.4
Liquid Products[d]									
Adults (70 kg)									
Postapplication Turf Activities	0.26	N/A	N/A	4.41	0.22	N/A	230 000	2350	18
Golfer		N/A	N/A	75.6	0.22	N/A	13 000	2350	23

Scenario	Drinking Water Exposure[a] (µg/kg bw/day)	Homeowners Applicator Exposure[d] (µg/kg bw/day)		Exposure from Re-entering Treated Turf[d] (µg/kg bw/day)			MOE[b]		ARI[c]
		Dermal	Inhalation	Dermal	Inhalation	Oral	Dermal	Inhalation/Oral	
Youth (39 kg)									
Postapplication Turf Activities	0.19	N/A	N/A	136	0.4	N/A	7000	2720	**19**
Golfer		N/A	N/A	7.91	0.4	N/A	130 000	2720	**27**
Children (15 kg)									
Postapplication Turf Activities	0.85	N/A	N/A	113	0.73	2.58	8850	197	**1.9**

[a] Drinking water exposure values are from Appendix V and are based on the highest modelled yearly value for water concentration For adults and children, the most conservative (Appendix IV, Table 4) and are based upon homeowners value from the adult and child subpopulations, respectively, was chosen. Homeowner applicator exposure values are from wearing short sleeved shirt, shorts and no gloves (except granular bait by hand and belly grinder); postapplication exposure values are from Appendix IV, Tables 5–7.

[b] MOE = NOAEL/exposure. Dermal NOAEL=1000 mg/kg bw/day from a 21-day dermal rabbit study and target MOE of 300. Inhalation NOAEL = 0.7 mg/kg bw/day from a 13-week dietary study in rats and target MOE of 100.

[c] ARI is not of concern when greater than 1. It was calculated using the following equation: ARI= 1/[(target MOE dermal/MOE dermal)+(target MOE inhalation/inhalation MOE)].

[d] There are no registered domestic liquid products, so homeowner application scenarios were not required for this formulation.

Appendix VII Water Modelling and Monitoring for Use in Drinking Water Risk Assessment

Modelling Results

EECs of dithiopyr in potential drinking water sources (groundwater and surface water) were estimated using Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of dithiopyr in groundwater were calculated using the LEACHM model to simulate leaching through a layered soil profile over a 50-year period. EECs of dithiopyr in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

The surface water EECs predicted by Level 1 modelling were large enough for Level 2 modelling to be conducted. The refinement for Level 2 modelling was to use a scenario representing turf instead of the standard Level 1 scenario. The Level 2 EEC estimate is thus crop-specific and does not allow for future use expansion into other crops. In this case, lower runoff from turf results in lower EECs. Table 1 provides a summary of the Level 1 and 2 modelled EECs for dithiopyr in potential sources of drinking water.

Table 1 Level 1 and 2 Estimated Environmental Concentrations of Dithiopyr in Potential Drinking Water Sources

Refinement Level	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Level 1	19	19	28	5.6	63	54.9
Level 2 (Ontario and Quebec only)	12.3	12.3	3.2	2	N/A[5]	N/A[5]

1 90th percentile of daily average concentrations.
2 90th percentile of yearly average concentrations.
3 90th percentile of yearly peak concentrations.
4 90th percentile of yearly average concentrations.
5 Dugout not included as regional scenarios for Ontario and Quebec only were used in Level 2 modelling.

Water Monitoring Data

Canadian Data

A search for dithiopyr water monitoring data in Canada found that limited information was available. A recent request was sent to the federal provincial and territorial representatives from all the provinces and territories in Canada, asking for water monitoring data for dithiopyr along with other active ingredients currently under re-evaluation. Any data received as a result of this request will be considered and the information contained here will be updated, if necessary.

Two datasets in the PMRA database contained data for dithiopyr. Both of these datasets contained data on various pesticide concentrations, including dithiopyr, in eight Canadian tributaries of Lake Ontario in 2000 and 2001. Of the 195 samples analysed in these 2 datasets, dithiopyr was not detected.

American Data

Data on residues present in water samples taken in the United States are important to consider in the Canadian drinking water assessment given the extensive monitoring programs that exist in the United States. Runoff events, local use patterns, site specific hydrogeology as well as testing and reporting methods influence more on residue data than the Northern versus Southern climate. As for the climate, if temperatures are cooler, residues may break down more slowly. On the other hand, if temperatures are warmer, growing seasons may be longer and applications may be more frequent.

American databases were searched for detections of dithiopyr. Both databases searched (the American NAWQA and USEPA STORET) did not contain information on dithiopyr. The NAWQA program does not have dithiopyr on the analyte list and no information was submitted to STORET for dithiopyr.

A study was conducted to investigate the impact of lawn-care pesticides on aquatic ecosystems and various pesticides were analysed in the water of six streams in the United States. The limits of quantitation for pesticides in water were set at 0.1 ng/L. Six water samples were collected quarterly from each stream from the summer of 2000 to the spring of 2002. Dithiopyr was detected in each stream at the concentrations and percentages reported below.

Summary of Dithiopyr Concentrations Detected in American Streams

Stream	% Detection	Maximum Concentration (ng/L)	Mean Concentration (ng/L)
Oak Newel	81	122.68	14.29
Keg Creek	71	252.50	21.75
Stoney Brook	76	142.92	12.72
Crabapple	81	243.43	22.60
Smoke Rise	76	184.56	16.59
Cherry Branch	82	179.58	21.44

A second study conducted to investigate the potential movement of dithiopyr following application to golf courses indicated that concentrations of dithiopyr in the leachate, transported through the greens, did not exceed 3 µg/L. The highest concentration of dithiopyr transported in runoff water from simulated golf course fairways did not exceed 40 µg/L. Generally, the concentration of dithiopyr in the runoff water was higher when applied as an emulsifiable concentrate formulation compared with the granule formulation.

Insufficient water monitoring data were available to estimate the potential exposure of dithiopyr to aquatic organisms and to humans through drinking water.

Appendix VIII Environmental Fate and Toxicity

Table 1 Environmental Fate of Dithiopyr

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products
Abiotic transformation					
Hydrolysis	Dithiopyr	30 d at 25°C	pH 5 stable pH 7 stable pH 9 stable	Not a major route of transformation	Monoacid (2%) at pH 9
Phototransformation - soil	Dithiopyr	Silt loam (pH 7.5, sand 24%, silt 68%, clay 8%, OM 0.74%)	5% transformed	Not a major route of transformation	Monoacid
Phototransformation - water	Dithiopyr	pH 7-8 (paddy water) and pH 7 buffered water at25°C, for equivalent of 36.4 d	16.7, 17.6 and 20.6 for paddy water, non-sensitized water and sensitized water, respectively	Major route of transformation	Monoacid, Reverse Monoacid, Diacid
Phototransformation - air	Dithiopyr	30 d at 30 °C	41.4 d	Route of transformation	None reported
Biotransformation					
Soil – aerobic	Dithiopyr	25°C; five soils: pH 6-8; % OC 0.58-5.37	Half-life: 523-2300 d	Persistent	Monoacid, Reverse Monoacid, Diacid
Soil - anaerobic	Dithiopyr	flooded two soils: pH 6; %OC 1.85-5.37	Half-life: 390-490 d	Persistent	Monoacid, Reverse Monoacid, Diacid
Aquatic - anaerobic	Dithiopyr	25°C; Kentucky water/sediment system	Half-life: 21732 d (largely adsorbed to sediment)	Persistent	
Bioaccumulation	Dithiopyr	Flow-through, bluegill sunfish	After 14 d depuration 92-94% was eliminated from the fish tissue	Not bioaccumulative	
Mobility					
Adsorption/ desorption	Dithiopyr	25°C; five soils from aerobic study and one extra silt loam: pH 6.9, 1.78% OM)	K_d 7.89-99.62 K_{OC} 1175-2482	Low mobility	

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products
Field studies					
Field dissipation	Dithiopyr	Four Canadian sites: Cambridge I, ON Cambridge II, ON St. Hiacynthe, PC Ayr, ON	Half-life: 4-8 d 0.6-1.2 d 11-20 d 6-217 d No radioactivity found below 15 cm depth	Non persistent	

Table 2 Environmental Toxicity of Dithiopyr

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
Terrestrial Species						
Invertebrate	Acute	Honey bee (*Apis mellifera*)	Dithiopyr	48 h LD_{50}	81 µg a.i./bee	Mortality
		Earthworm (*Eisenia foetida*)	Dithiopyr	14 d LC_{50} NOEC	> 1000 mg a.i./ kg soil > 1000 mg a.i./ kg soil	Mortality
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	Dithiopyr	LD_{50}	> 2250 mg a.i./ kg bw	Mortality
	Dietary	Bobwhite quail (*Colinus virginianus*)		LC_{50} NOEC	>5620 mg a.i./ kg diet 3160 mg a.i./ kg diet	Mortality
		Mallard duck (*Anas platyrhynchos*)		LC_{50} NOEC	>5620 mg a.i./ kg diet 5620 mg a.i./ kg diet	Mortality

Organism	Study type	Species	Test material	Endpoint	Value (effect)	Effect of concern
	Reproduction	Bobwhite quail (*Colinus virginianus*)		NOEC	1250 mg a.i./ kg diet	Reproduction
		Mallard duck (*Anas platyrhynchos*)		NOEC	1250 mg a.i./ kg diet	Reproduction
Mammals	Acute oral	Rat	Dithiopyr	LD_{50}	>5000 mg a.i./ kg bw	Mortality
		Mouse		LD_{50}	>5000 mg a.i./ kg bw	Mortality
	Dietary	Rat		90 d NOEC	0.66 mg a.i./ kg diet	Growth
		Mouse		90 d NOEC	1.16 mg a.i./ kg diet	Growth
	Reproduction	Rat		NOEC	25 mg a.i./kg diet	Reproduction
Plants	Seed germination	10 plant species	Dithiopyr (rate 9-2240 g a.i./ha)	NOEC	82.9-2240 g a.i./ha	Germination
	Seedling emergence			EC_{25} NOEC	2.9-2240 g a.i./ha 3.5-2240 g a.i./ha	Plant height and plant dry weight
	Vegetative vigour			EC_{25} NOEC	45.9-593.6 g a.i./ha 28-2240 g a.i./ha	Plant hight, plant dry weight and percent survival
Freshwater Organisms						
Invertebrate	Acute	*Daphnia magna*	Dithiopyr	48-h LC_{50}	1.1 mg a.i./L	Immobility
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	Dithiopyr	96-h LC_{50}	0.48 mg a.i./L	Mortality
		Bluegill sunfish (*Lepomis macro chirus*)	Dithiopyr	96-h LC_{50}	0.75 mg a.i./L	Mortality
	Early Life Cycle	Rainbow trout (*Oncorhynchus mykiss*)	Dithiopyr	NOEC LOEC	0.056 mg a.i./L 0.12 mg a.i./L	-
Algae	Acute	Green alga (*Selenastrum capricornutum*)	Dithiopyr	EC_{50} NOEC	52.9 µg a.i./L 20.8 µg a.i./L	Growth and inhibition

Table 3 Summary of Screening Level Risk Assessment of Dithiopyr to Terrestrial Organisms

Organism	Exposure	Endpoint reported	Use Rate (g a.i./ha)	EEC	RQ[1]
Invertebrates					
Earthworm	Acute	NOEC = 1000 mg a.i./kg soil	558	0.25 mg a.i./kg soil	2.5×10^{-4}
Honeybee	Acute contact	NOEC = 8.1 mg a.i./bee (9.07 kg a.i./ha)		558×10^{-3} kg a.i./ha	6.1×10^{-2}
Birds					
Bobwhite quail	Dietary	LC_{50} = 5620 mg a.i./kg diet	558	97.7 mg a.i./kg diet	3.1×10^{-2}
	Reproduction	NOEC = 1250 mg a.i./kg diet			7.8×10^{-2}
Mallard	Dietary	LC_{50} = 5620 mg a.i./kg diet	558	18.87 mg a.i./kg diet	3.4×10^{-3}
	Reproduction	NOEC = 1250 mg a.i./kg diet			1.5×10^{-2}
Mammals					
Mouse	Dietary	NOEC= 1.16 mg a.i./kg diet	558	279.8 mg a.i./kg diet	**241**
Rat	Dietary	NOEC = 0.66 mg a.i./kg diet		281.5 mg a.i./kg diet	**427**
	Reproduction	NOEC = 25 mg a.i./kg diet			**11**
Plants					
Plants	Seedling emergence (onion)	EC_{25} = 2.9 g a.i./ha	558	558 g a.i./ha	**192**
	Vegetative vigour (ryegrass)	EC_{25} = 45.9 g a.i./ha	558	558 g a.i./ha	**12**

[1] Bold fonts indicates exceedance of LOC.

Table 4 Refined Risk Assessment of Dithiopyr to Terrestrial Organisms

Organism	Exposure	Toxicity endpoint	Use Rate (g a.i./ha)	Drift EEC* (g a.i./ha)	RQ[†]
Mammals	Dietary	0.66 mg a.i./kg diet	558	33.5	**26**
	Reproduction	25 mg a.i./kg diet			0.7
Plants	Seedling emergence (onion)	EC_{25} = 2.9 g a.i./ha			**11.5**
	Vegetative vigour (ryegrass)	EC_{25} = 45.9 g a.i./ha			0.7
	Species Sensitivity Distribution analysis	HC_5 = 4.765 g a.i./ha			7

* Based on drift of 6% for a default droplet size of medium (herbicides).
† Bold fonts indicates exceedance of LOC.

Table 5 Summary of Screening Level Risk Assessment of Dithiopyr to Aquatic Organisms

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	Use Rate (g a.i./ha)	EEC** (mg a.i./L)	RQ[†]
Freshwater Species							
Invertebrate	Acute	*D. magna*	LC_{50} = 1.1	0.55	558	7×10^2	1.3×10^1
Fish	Acute	Rainbow trout	LC_{50} = 0.48	0.048	558	7×10^2	**1.46**
	Early Life Cycle	Rainbow trout	NOEC = 0.056	0.056			**1.25**
Amphibian	Acute	Rainbow trout (surrogate)	LC_{50} = 0.48	0.048	558	3.7×10^1	**7.7**
	Early Life Cycle	Rainbow trout (surrogate)	NOEC = 0.056	0.056			**6.6**
Plant	Acute	Green alga	NOEC = 0.021	0.021	558	7×10^2	**2.1**

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
** EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.
† Bold fonts indicates exceedance of LOC

Table 6 Refined Risk Assessment of Dithiopyr to Aquatic Organisms from Spray Drift

Organism	Exposure	Toxicity endpoint (mg a.i./L)	Use Rate (g a.i./ha)	Drift EEC* (mg a.i./L)	RQ
Fish	Acute	0.048	558	0.0042	< 0.1
	Early Life Cycle	0.056			< 0.1
Amphibians	Acute	0.048	558	0.022	0.45
	Early Life Cycle	0.056			0.39
Plants	Acute	0.021	558	0.0042	0.16

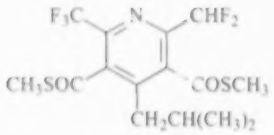
* Based on drift of 6% for a default droplet size of medium (herbicides).

Table 7 Risk Assessment of Dithiopyr for Freshwater Organisms from Predicted Run-Off

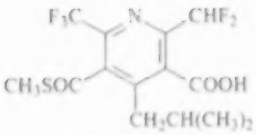
Toxicity endpoint	EEC (µg a.i./L)*	Endpoint (µg a.i./L)	RQ
Amphibians			
Acute	11.7	48	0.24
Early Life Cycle	1.6	56	<0.1
Fish			
Acute	2.4	48	<0.1
Early Life Cycle	1.4	56	<0.1
Algae			
Acute	2.4	26	<0.1

* 90th percentile of peak and 21d runoff values for acute for chronic, respectively.

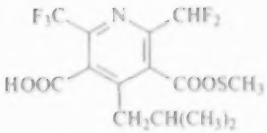
Appendix IX Structure of Dithiopyr and Its Transformation Products



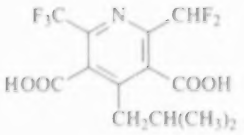
Dithiopyr



Monoacid



Reverse Monoacid



Diacid

Appendix X Label Amendments for Commercial Class Products Containing Dithiopyr

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary personal protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

The labels of end-use products in Canada must be amended to include the following statements to further protect workers and the environment.

Add to ENVIRONMENTAL HAZARDS section:

> **TOXIC** to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under **DIRECTIONS FOR USE**.

Add to PRECAUTIONS section:

> For all uses, except golf courses, **DO NOT** enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. For golf courses, **DO NOT** enter or allow worker entry until after the spray has dried.

Add to DIRECTIONS FOR USE section:

Only one application per year is permitted.

> Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.
>
> **DO NOT** apply by air.
>
> **Buffer zones:**
>
> Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

For application to rights-of-way, buffer zones for protection of sensitive terrestrial habitats are not required; however, the best available application strategies which minimize off-site drift, including meteorological conditions (e.g. wind direction, low wind speed) and spray equipment (e.g. coarse droplet sizes, minimizing height above canopy), should be used. Applicators must, however, observe the specified buffer zones for protection of sensitive aquatic habitats.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of Application	Buffer Zone (metres) Required for the Protection of:		
	Terrestrial Habitat	Aquatic Habitats of Water Depths:	
		<1 m	>1 m
Field sprayer*	4	1	1

* For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

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A. Impact on Human and Animal Health

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Upublished Information

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B. Impact on the Environment

Studies/Information Provided by the Applicant/Registrant (Unpublished)

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Additional Information

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